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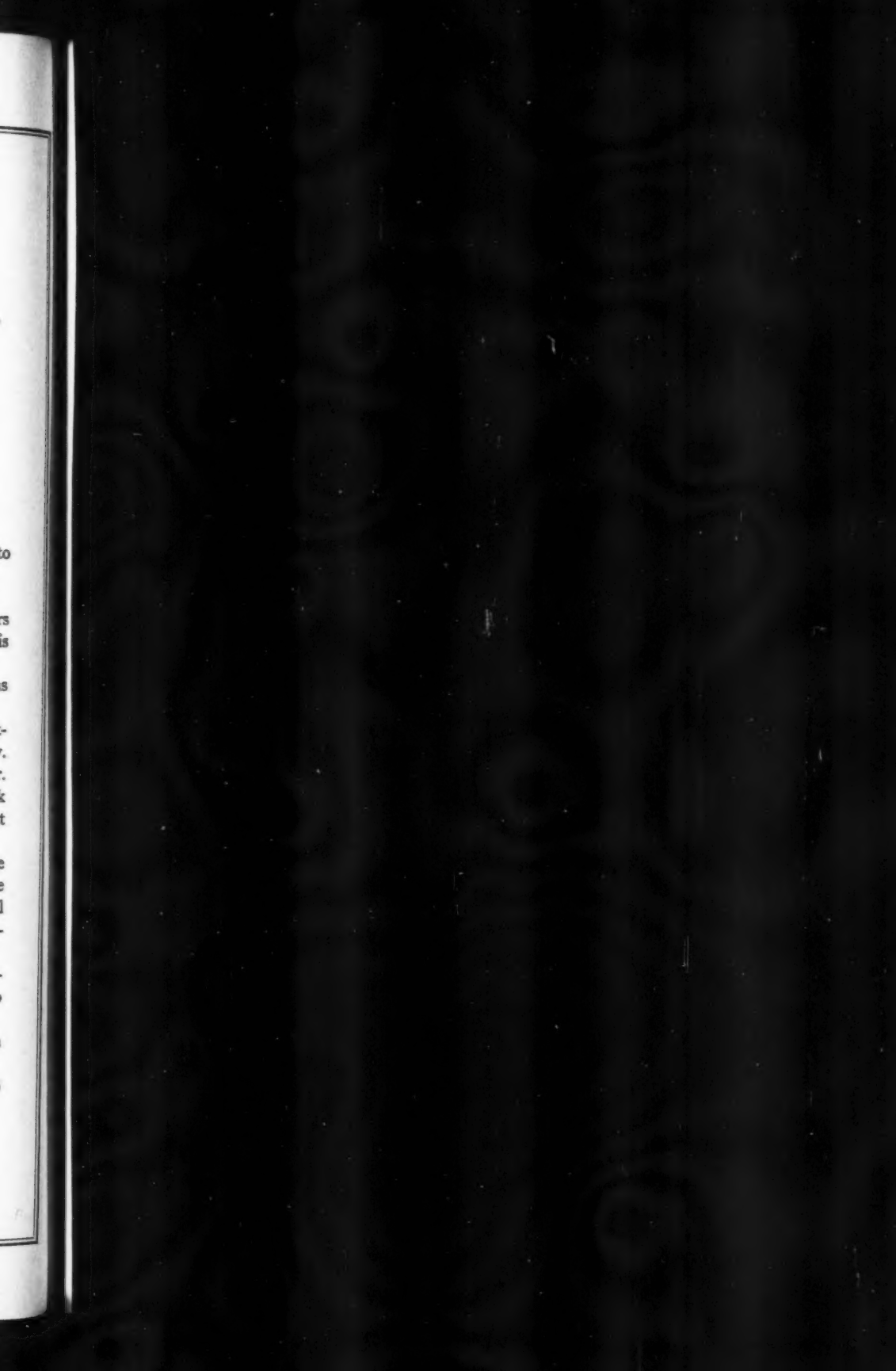

THE AGGLUTINATION OF HEMOLYTIC STREPTOCOCCI BY PLASMA AND FIBRINOGEN

A Comparison of the Phenomenon to Serological Reactions with the Same Organisms

WILLIAM S. TILLETT and R. L. GARNER

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Submitted for publication August 24, 1933

In a previous report (1) results were presented which demonstrate that sera from many cases of acute bacterial infections are capable of agglutinating certain strains of hemolytic streptococci. When suitable cultures are tested with appropriate sera, the bacterial cells form coarse clumps which, in gross appearance, cannot be differentiated from specific antibacterial serological reactions. In spite of this fact, the phenomenon described presented certain characteristics strongly suggesting that the underlying mechanism did not represent a specific antigen-antibody relationship. The results upon which this conclusion is based may be briefly described as follows:

1. *Absence of serological specificity.* Sera from patients suffering from acute infections of diverse etiology agglutinated hemolytic streptococci. For example, sera from cases of pneumococcus pneumonia or typhoid fever were highly reactive.

2. *Parallelism between activity of acute disease and serological reactivity.* When repeated tests were made during the course of an acute infection, the capacity of serum to cause a clumping of streptococci was found to appear early after onset, to persist during the active phase of infection, and to disappear very soon after recovery. This time relationship differs from the well-known immune response exhibited by patients, who, late in bacterial disease, develop antibodies which are specific for the etiological agent, and which persist for several weeks or months.

3. *Separation, by serum fractionation, of streptococcus reacting factor*

from specific antibody. By chemical fractionation, the portion of serum reactive with hemolytic streptococci was found to be different from that ordinarily associated with bacterial antibodies. Sera from cases of typhoid fever were employed and the fraction of serum agglutinating hemolytic streptococci was separated from the agglutinin for typhoid bacilli (Widal Reaction) present in the same serum.

4. *Effect of heat on agglutinability of organisms.* Heating cultures to the thermal death-point (56°C. for 15 to 60 minutes) destroys reactivity. The heat lability of this property of streptococci differs from the heat stabile antigenic integrity exhibited by the bacterial cells when tested with specific anti-streptococcal antibodies.

The underlying mechanism, therefore, responsible for the clumping of hemolytic streptococci by sera from cases of acute bacterial disease, seems to depend upon some property of the blood which is not normally present in serum but which is evoked by acute bacterial insults, and is demonstrable as an agglutinin-like substance when tested with certain susceptible cultures of hemolytic streptococci.

In continuing an investigation of this streptococcal reaction, tests have been performed with plasma and fibrinogen, as well as with serum. Results have been obtained which suggest in part the nature of the serological reactions formerly described. The purpose of this communication is to describe in more detail observations, previously mentioned (2), which concern the agglutinative action of plasma and fibrinogen on hemolytic streptococci, and also to present experiments which were designed to compare the agglutinative constituent present in serum with that present in plasma.

MATERIALS AND METHODS

Strains of hemolytic streptococci employed. The strains of *streptococcus hemolyticus* which are reactive with plasma and fibrinogen are of the Beta hemolytic type (3); and are the same as those giving positive tests with patients' sera (1, 2). All strains of hemolytic streptococci are not agglutinable. The cultures that have proven satisfactory were derived from different disease sources. Reactivity seems to depend upon some property of the organisms the exact nature of which has not yet been determined. The scarlet fever strain of Dr. A. R. Dochez, designated N. Y. 5, has been employed in most of the tests. This strain has been in artificial cultivation for many years.

Culture media. NaCl meat infusion broth, adjusted to pH 7.6 and containing

0.02 to 0.05 per cent dextrose, has been found to be the most satisfactory medium. The broth contains 1 per cent peptone but is not buffered. The final pH, after growth has occurred, rarely goes below 7.2. Fresh 18- to 24-hour living broth cultures were always employed.

Technique for testing plasma and fibrinogen. Serial dilutions of plasma and fibrinogen were made according to the same procedure employed in serological titration. Each tube contained 0.5 c.c. of the various dilutions of plasma or fibrinogen, and 0.5 c.c. of culture was added to each. The tubes were thoroughly shaken. Final readings were made after incubation in the water-bath at 37.5°C. for two hours and at icebox temperature overnight. In obtaining accurate titrations it was found necessary to use a separate pipette for each serial dilution. When the same pipette was employed for a set of tubes, the results were usually higher and often inconstant. Fibrinogen and plasma seem to possess a cohesive quality through which they adhere to the pipette and are washed off irregularly as the serial mixtures are made.

Anticoagulants. Potassium oxalate was employed in most of the tests, 0.02 gm. to 10 c.c. of blood. 1 c.c. of a 2 per cent solution was placed in small bottles which were heated in a dry-air sterilizer until the oxalate was deposited as a dry powder on the bottom of the bottle. Unless otherwise specified, oxalate was the anticoagulant regularly used. Sodium citrate was similarly prepared.

Heparin was used also, 1 mgm. per 5 c.c. of blood.

Hirudin was employed, 1 or 2 mgm. per 5 c.c. of blood.

Preparation of fibrinogen. Fibrinogen was chemically isolated from plasma by salting out with an equal volume of a saturated solution of NaCl and also with ammonium sulphate at 25 per cent saturation. By the NaCl process, a greater and more satisfactory yield is obtained by carrying out the procedure in a cold atmosphere with chilled materials. With slight modification the methods were the same as those described by Pickering (4) and by McLean (5), and recorded in standard textbooks of Physiological Chemistry.

When plasma and suitable cultures are mixed according to the technique employed in serological titration, a coarse conglomeration of organisms occurs which is often readily visible after a few minutes. The degree of coarseness of the clumping usually increases rapidly until, after 30 minutes, masses collect at the bottom of the tube, which are only partially broken up by shaking. In other instances the rate of reaction is slower and the degree of clumping less gross, but final readings have not shown significant qualitative differences among the samples of plasma.

A striking feature of the reaction is the high dilutions of plasma at which clumping of hemolytic streptococci may be detected. The

TABLE I

Agglutination of hemolytic streptococci by plasma

PATIENT	DISEASE	TITRE OF SERUM	DILUTIONS OF PLASMA							
			1:10	1:100	1:1,000	1:10,000	1:20,000	1:40,000	1:80,000	1:160,000
St	Lobar pneumonia type II	1:2,000 +	++++	++++	++++	++++	++++	+++	++	—
Da	Typhoid fever	1:5,000 +	++++	++++	++++	++++	++++	++	+	—
Sc	Pulmonary tbc.	—	+++	++++	++++	++++	++	++	+	—
Wi	Lobar pneumonia group IV	1:1,000 +	+++	++++	++++	++++	++	+	±	—
Wi	Same 10 days later	—	+++	+++	++++	+++	++	+	±	—
Ti	Normal	—	+++	+++	+++	+++	++	+	±	—
Ga	Normal	—	++	+++	+++	+++	+	−	−	—

Tests were done with living organisms. Tubes were incubated at 37.5°C. for two hours and placed in icebox overnight.

TABLE II

Agglutination of hemolytic streptococci by fibrinogen

		DILUTIONS OF TEST MATERIAL						
		1:10	1:100	1:1,000	1:10,000	1:20,000	1:40,000	1:80,000
Case of typhoid fever	Plasma (oxalated)	++	++++	++++	++++	+++	++	±
Case of typhoid fever	Fibrinogen—50 per cent saturation NaCl	±	++++	++++	+++	±	−	−
Case of typhoid fever	Fibrinogen—25 per cent saturation $(NH_4)_2SO_4$	++	++++	++++	+++	+	−	−
Normal	Plasma (oxalated)	+++	+++	+++	+++	++	+	−
Normal	Fibrinogen—50 per cent saturation NaCl	++	++++	++++	++	±	−	−
Normal	Fibrinogen—25 per cent saturation $(NH_4)_2SO_4$	++	+++	+++	+	−	−	−

Tests were done with living organisms. Tubes were incubated at 37.5°C. for two hours and placed in icebox overnight.

titres recorded in table I range from 1 to 20,000 to 1 to 80,000. This result indicates the small amount of the active principle present in plasma which is capable of rendering the bacterial cells cohesive.

Tests have been carried out with plasma from normal individuals and from patients acutely ill with bacterial infections. The results presented in table I were obtained by the use of oxalated blood, which has been regularly employed. Comparative tests have been done with plasma of citrated, heparinized, and hirudinized blood. The titre of agglutination has been the same in each instance. It is, therefore, unnecessary to give the results in detail.

The data contained in table I have been selected from a larger number of tests to demonstrate not only the aggregating effect of plasma on hemolytic streptococci but also to bring out certain characteristics of the bacterial clumping caused by plasma in relation to serological agglutination. In the first place it should be emphasized that normal plasma, as well as that from patients, agglutinates suitable cultures of hemolytic streptococci in high dilutions. This result is of special interest, in view of the fact that normal sera have been found to be uniformly negative. The capacity of human plasma to conglomerate the streptococci is qualitatively the same in all the tests. Quantitative estimations indicate that the plasma from cases of acute infection tend to have a titre slightly higher than that of normal persons. Convincing proof, however, that this minor variation is definitely significant, fails to be established by repeated tests carefully performed according to the procedure described in the paragraph on *Technique of Test.* Comparable titration experiments with plasma leave in doubt the question whether the differences between agglutination tests with patients' and with normal sera are reflected in variations in plasma reactivity. The two tests which were done with the blood of patient Wi (table I) show the presence of agglutinating substances in the serum taken during active disease, and their disappearance following recovery. The titre of plasma, however, taken on the same two occasions was unchanged.

The high titre of agglutinating substance in plasma—even from normal persons—in contrast to the uniformly negative results with normal serum, led to an investigation of the agglutinating activity of fibrinogen, the most important protein present in plasma but absent from serum.

When solutions of fibrinogen, chemically derived from plasma, were titred in the usual way with reactive cultures of hemolytic streptococci, the organisms were clumped in small aggregates, which were, in gross appearance, similar to that induced both by plasma and by serum from patients.

Table II contains the results of agglutination tests performed with hemolytic streptococci and fibrinogen derived from the plasma of a case of typhoid fever and from a normal individual. The fibrinogen was removed both by sodium chloride and by ammonium sulphate precipitation. The results presented in the table are representative of many tests similarly performed.

The character of the bacterial clumping caused by fibrinogen solutions is qualitatively identical with the agglutination of hemolytic streptococci by plasma. The titre of fibrinogen activity is slightly less than that of plasma; a difference which undoubtedly depends upon the incompleteness of chemical precipitation of fibrinogen. The result of these tests indicate, therefore, that the active principle in plasma responsible for the coherence of the organisms into clumped masses is either fibrinogen itself or some closely allied substance.

In the former report on serological reactivity of hemolytic streptococci it was stated that some strains were susceptible to clumping and that others remained diffuse when mixed with the same sera. Furthermore, it was found that killing the organisms by heat destroyed agglutinability, whereas formalin had no effect. Experiments were therefore carried out to determine whether the same conditions that determined serological results also held for the conglomeration of streptococci by plasma and fibrinogen. Comparable tests were performed with known reactive serum, with plasma, and with fibrinogen. Living cultures of agglutinable and non-agglutinable strains of streptococci were employed; the strains were also heat-killed and killed with 0.3 per cent dilution of formalin. The results are contained in table III.

The results of agglutination tests with serum, plasma, and fibrinogen demonstrate that the conditions which preserve the bacterial property of reactivity (living or formalinized) are applicable in all the tests; and that killing by heat destroys the agglutinability of the organisms in either serum, plasma, or fibrinogen. This parallelism indicates that

TABLE III

Titration of living, heat-killed, and formalinized cultures of hemolytic streptococci (agglutinable and non-agglutinable) with serum, plasma, and fibrinogen

STRAIN	CONDITION OF CULTURE	TITRATION OF												
		Serum*			Plasma†					Fibrinogen‡				
		1:10	1:100	1:1,000	1:10	1:100	1:1,000	1:10,000	1:100,000	1:10	1:100	1:1,000	1:10,000	1:100,000
NY5	Living broth culture	++++	++++	++	++	++++	++++	+++	±	++++	++++	++++	++	−
	Heated 56°C. for 1 hour, killed	−	−	−	−	−	−	−	−	−	−	−	−	−
	0.3 per cent formalin, killed	++++	++++	+	++	++++	++++	+++	−	++++	++++	++++	+	−
Ma	Living	+++	+++	+	++++	++++	++++	++	−	++++	++++	+++	±	−
	Heated 56°C. for 1 hour, killed	++	±	−	−	−	−	−	−	−	−	−	−	−
	0.3 per cent formalin, killed	++++	++	+	+++	++++	+++	++	−	+++	+++	+++	+	−
Le	Living	−	−	−	−	−	−	−	−	−	−	−	−	−
	Heated 56°C. for 1 hour, killed	++	−	−	−	−	−	−	−	−	−	−	−	−
	0.3 per cent formalin, killed	++	+	−	−	−	−	−	−	−	−	−	−	−
Ab	Living	−	−	−	−	−	−	−	−	−	−	−	−	−
	Heated 56°C. for 1 hour, killed	−	−	−	−	−	−	−	−	−	−	−	−	−
	0.3 per cent formalin, killed	−	−	−	−	−	−	−	−	−	−	−	−	−

* Serum obtained from patient acutely ill with lobar pneumonia.

† Oxalated plasma from normal adult.

‡ Fibrinogen derived from normal plasma by salting out with NaCl.

the bacterial element possessed by the agglutinable cultures of hemolytic streptococci is the same regardless of the blood component utilized in the tests. The results also strongly suggest that the agglutinating substance in patients' sera is closely allied to fibrinogen which is the principle reactive constituent of plasma.

That the reactive material in a patient's serum might be fibrinogen necessitates the assumption that, in the coagulation of blood from the patient, a small increment of fibrinogen remains unchanged into fibrin and "spills over" into the serum. In this connection it is interesting to note that several authors (6, 7, 8) report that the blood fibrinogen is quantitatively increased in acute infections. Furthermore, Maltaner and Johnston (9), and Kyes and Carey (10), have been able to demonstrate fibrinogen in the *sera* of certain animals. The first named authors, in an investigation of the phenomenon of conglutination, were able to induce "secondary" clots in bovine serum by the addition of platelets. Kyes and Carey prepared fibrinogen-free fowl serum by adding $CaCl_2$ and cephalin to oxalated plasma. On the basis of the possibility that the serum of patients might contain a very small amount of fibrinogen, the methods of removing fibrinogen employed by both Maltaner and Johnston and by Kyes and Carey have been utilized with the sera of patients which are highly reactive with streptococci. In all of the attempts it was found that the serum, after treatment, possessed the same titre of agglutinable substances as the untreated sample. By this method, therefore, it has been impossible to eliminate the clumping power of serum and so directly prove that the reactive factor in serum is fibrinogen.

Furthermore, thrombin, prepared according to a method described elsewhere (11), has been added to agglutinating serum for the purpose of changing any fibrinogen, which might be present, into fibrin. Appropriate serum, to which thrombin is added, did not contain visible strands of new-formed fibrin, and the agglutinating titre was not affected.

The second method of attempting to identify the active principle in serum consisted of salting out protein fractions by different concentrations of ammonium sulphate and testing each fraction for the capacity to agglutinate the cultures.

From the table it may be seen that the fraction of serum which

flocculates at 25 per cent and 27.5 per cent saturation with ammonium sulphate contains almost all of the reactive factor. These salt concentrations, when applied to plasma, precipitate fibrinogen, and to a less extent other closely related globulins. Furthermore, with the 25 per cent and 27.5 per cent salt saturations of reactive sera, there was a distinctly greater yield of precipitate from a serum known to be reactive with streptococci than was obtained from normal serum. In

TABLE IV

Agglutination of hemolytic streptococci by serum proteins, fractionated from patients' sera by different concentrations of $(NH_4)_2SO_4$

	DILUTIONS OF SERUM FRACTIONS					
	1:10	1:50	1:100	1:500	1:1,000	1:5,000
per cent						
Whole serum*	++++	++++	++++	++++	++	±
25	++++	+++	+++	+	−	−
27.5	+++	++	±	−	−	−
30	−	−	−	−	−	−
35	−	−	−	−	−	−
40	−	−	−	−	−	−
50	−	−	−	−	−	−
Whole serum†	++++	++++	+++	++	±	−
27.5	++++	++++	++	+	−	−
30	++	−	−	−	−	−
35	±	−	−	−	−	−
40	−	−	−	−	−	−
45	−	−	−	−	−	−

Tests were done with living organisms. Tubes were incubated at 37.5°C. for two hours and placed in icebox overnight.

*Serum from case of bronchopneumonia.

†Serum from case of lobar pneumonia.

the former, white particulate substances formed in appreciable amounts which could be centrifuged out, and redissolved in physiological salt solution. With normal serum, a diffuse cloud formed which could not be removed by centrifugation.

The results with blood protein fractions precipitated from serum with different concentrations of $(NH_4)_2SO_4$, indicate that: (1) the agglutinating factor flocculates with the concentrations which ordinarily affect fibrinogens and closely related proteins and (2) the

amount of particulate matter derived from a patient's serum is distinctly greater than that obtainable from normal serum. Accurate quantitative measurement of the difference has not yet been accomplished.

DISCUSSION

The results recorded in this report demonstrate that plasma, in high dilutions, is capable of causing the bacterial cells of certain strains of hemolytic streptococci to form moderately coarse clumps. Furthermore, the reactive principle of plasma is found to reside chiefly in the fibrinogen.

Both in the experiments described in this article and in those previously reported (1, 2) susceptibility to agglutination was not found in all strains of hemolytic streptococci. A study of the relationship between the source of strains and agglutinability is now in progress and will be subsequently reported.

The clumping of suitable cultures by plasma or fibrinogen has been interpreted as an interaction between streptococci and certain plasma proteins, through which the bacterial cells become cohesive and adhere together in aggregates. The agglutination under these experimental conditions, although indistinguishable from specific bacterial antigen-antibody reactions in so far as cellular aggregation is concerned, is probably of a somewhat different physico-chemical order.

Other investigators have studied the aggregating effect of plasma on cells, both with erythrocytes (sedimentation rate) and with bacteria. The voluminous literature on the occurrence and mechanism of the suspension stability of red cells cannot be entered into here other than to mention the fact that changes in suspension stability are associated with a clumping of the cells induced by special physico-chemical properties of fibrinogen or closely related blood proteins. The nonspecific aggregating of bacterial cells by plasma has much in common with the increased sedimentation of red blood cells. Results suggesting a close association were formerly described (1). Such a comparative study has been reported earlier by Vorschütz (12) and by Mandelstamm (13), and more recently by Reimann (14). Reimann attributed the effect of plasma on both bacteria and red cells to a changed viscosity, and suggested a correlation between this altered state of the

blood and defense against infection. Hitchcock and Swift (15) have recently reported on the agglutinating properties of exudates from cases of rheumatic fever. They detected the effect of the exudate on hemolytic streptococci and staphylococci by using the thread reaction, and they suggest that the clumping is possibly associated with a globulin similar to fibrinogen.

The reports of other investigators as well as the results in this laboratory indicate that the humoral portion of whole uncoagulated blood is possessed of certain properties which may affect the surface of bacterial cells and cause cohesion. Furthermore, this property is especially manifest early after the beginning of acute infection, and is, in the absence of true serological antibodies, a non-specific phenomenon.

The particular problem of non-specific agglutination, with which this article deals, concerns the aggregating effect on hemolytic streptococci of blood constituents which are present in the plasma of normal persons as well as of acutely ill patients, but, with serum, is demonstrable only in that derived from patients. A comparative study of the plasma and serum reactions is as yet inconclusive, but the results suggest that reactive sera contain a protein closely allied to fibrinogen, which is the chief agent responsible for the aggregation of streptococci by plasma. The final proof that a blood protein is fibrinogen rests on its transformation into fibrin. Since our attempts to induce fibrin formation in reactive sera have failed, the identification of the agglutinating substance as "excess" fibrinogen has so far been unsuccessful. Salting out the active serum factor with 25 per cent and 27.5 per cent saturation with $(NH_4)_2SO_4$, however, points to a fibrinogen-like protein as the responsible fraction. It seems not impossible that this fibrinogen-like globulin may be a blood protein which, like fibrinogen, is capable of clumping hemolytic streptococci, but is so chemically constituted as to be unable to form fibrin. This difference, therefore, may account for its presence in serum.

CONCLUSIONS

1. Plasma from normal individuals and from patients is capable of agglutinating, in very high dilutions, certain strains of hemolytic streptococci.

2. Fibrinogen, chemically isolated from plasma, also agglutinates the same strains of hemolytic streptococci and is considered to be chiefly responsible for the reactivity of plasma.

3. Only those strains of hemolytic streptococci that are agglutinated by sera from cases of acute infection are visibly affected by plasma or fibrinogen; killing the organisms by heat destroys their reactivity in plasma and fibrinogen, as well as in serum; cultures, killed with formalin, remain susceptible to the effect of each of the three blood constituents.

4. The reactive fraction in the sera of patients seems to be a blood protein closely related to fibrinogen.

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THE HYPOPHYSIS OF THE HUMAN CASTRATE

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The recent intensive physiological work on the anterior lobe of the hypophysis cerebri and its relation to sex has made it necessary to restudy the histological aspects of the gland in an attempt to find some morphological criteria for the variations in its function. The literature abounds in contradictions, very largely due to the variations in staining technique used by the different authors.

It is now a well established fact that castration in the albino rat is followed by the appearance of large vacuolated basophile cells in the anterior lobe of the hypophysis, and coupled with the increased potency of the castrate's hypophysis it has generally been assumed that these cells manufacture and store at least one of the gonadotropic hormones. However, in the present state of our knowledge and with the diverse reports of the changes, or absence of changes, in this gland following castration it is evident that generalisations from species to species are impossible.

The first to describe castration changes in the hypophysis was Fichera (1). He stated that following castration in the domestic fowl the hypophysis increased in size. Histologically, he found an increase in size and number of the eosinophiles. Similar changes were described in cattle and European buffaloes.

Cimorini's (2) findings in his work on dogs and rabbits substantially agree with those of Fichera. Marrassini (3), however, found no constant histological changes in the hypophyses of castrated dogs, sheep, cattle, rabbits or guinea-pigs. Kuhn (4) failed to find any increase in size in castrated horses, and Livingston (5) concludes that there is no constant hypophyseal hypertrophy following castration in rabbits.

Biedl (6) first pointed out the development of peculiar clear cells

in the hypophysis of castrated albino rats. This was further studied by Anderson (7), who traced the development of these cells from the basophiles of the anterior lobe, and these latter in turn from the chromophobes. This observation has now been frequently confirmed, and the albino rat remains as the one castrate animal in regard to which the descriptions of the hypophyseal changes in the literature are in general agreement.

In spite of the fact that there must have been many autopsies performed on castrated human beings following the periods in which castration was considered a cure for prostatic hypertrophy, and bilateral oöphorectomy was a relatively frequent operation, the studies on the human hypophysis in this relationship are surprisingly few.

In 1907 Tandler and Gross (8) observed roentgenologically an increase in the size of the sella turcica in castrates. Koch (9) in his examination of the *Skoptzis*—a religious sect whose religion prescribes that male members be castrated—described a similar change.

The first histological description of a human hypophysis in these circumstances seems to be that of Kon (10). This author describes an increase in the number of eosinophiles, and in one of his cases an enlargement of the chromophobes. His work was supported a few years later by Rössle (11), who arrived at the conclusion that castration in man is followed by an increase in size of the hypophysis, histologically shown to be due to an increase in the number of eosinophile cells, with heterotopic formation of eosinophiles in the periphery of the gland, and an absence or decrease in the number of basophiles. Kolde (12), in a review of the changes in six cases, records an increase in both basophiles and eosinophiles.

It will thus be seen that the description of the castrate hypophysis varies from species to species. The majority of authors report its enlargement, and except for the albino rat, wherever histological changes are admitted, they consist in an increase of the acidophile cells.

In a review of some hundred hypophyses the following four cases of castration in human beings were encountered.

The material had been fixed in Zenker-formol. Serial sections were cut at 5 microns, and the sections stained with Mann's methyl-blue-eosin stain. It was found that the best differentiation could be obtained by staining for 2 to 12 hours, removing excess stain quickly in

water, and then immersing in absolute alcohol until the clouds of eosin cease coming out. If the basophiles are overstained a longer immersion in the alcohol should be given. The stain gives a beautiful differentiation between the three groups of cells in the anterior lobe. The method has been checked against the acid-fuchsin-acid-violet method of Bailey, and the acid-fuchsin-acid-violet-methyl-green method recently published by Severinghaus. The staining reaction corresponds in its differentiation of the three cardinal groups of cells to that given by these other methods. I am indebted to Dr. F. B. Kindell of this department for this technique.

Case 1. Autopsy 10240. Coloured female, aged 44 years. Weight 60 kilograms. Operation three years previously for removal of uterus, tubes and ovaries.

Anatomical diagnosis: History of hypertension; tonsillectomy; chronic arteriolosclerotic nephritis with exacerbation following infection; old tuberculosis of the right lung with dense pleural adhesions; oedema of both lungs; absence of uterus, tubes and ovaries.

Microscopic examination: Adrenals: These do not seem enlarged. The cortex shows no adenomatous formation. It has a high fat content. The medulla is not remarkable.

Thyroid: The thyroid is essentially normal, being composed of medium-sized colloid acini with a lining of flat epithelium.

Hypophysis: This does not seem to have been much enlarged. The outstanding characteristics of the sections is the great number of basophile cells. These are scattered diffusely throughout the whole gland, being aggregated into masses here and there sufficiently large to occupy a whole high-power field. Many of these cells show one or more clear vacuoles in their cytoplasm, and a few contain droplets of colloid. The eosinophiles do not seem diminished in number, being quite numerous and large. The chromophobe cells are of two types—a small non-granular cell with scanty cytoplasm, representative of the usual type, and a larger type with copious cytoplasm equal in size to the cells of the chromophile series. Study of these cells shows that a few of them may show the presence of basophile granules in the cytoplasm, and with search the stages between the non-granular cell and the densely packed basophile cell can be found. Serial sections show that the increase in basophiles is general throughout the gland, and while they tend to give way to eosinophiles in the lateral lobes, even in this site they are more numerous than usual. Near the periphery of the gland is a small chromophobe adenoma. There are a few cysts filled with colloid in the region of the pars intermedia, but no more so than is commonly seen in adult glands. There is no invasion of the pars nervosa by basophiles.

Case 2. Autopsy 10638. White male, aged 58. Weight 78 kilograms. Bilateral orchidectomy two years before death for tuberculosis of the testes.

Anatomical diagnosis: Tuberculosis of the right kidney, ureter and bladder; Pott's disease of the spine; tubercles in lung, liver and spleen; acute splenic tumour; arteriosclerosis; absence of both testes and left kidney.

Microscopic examination: Adrenals: These appear normal in size. The zona glomerulosa is relatively distinct. The fat content of the remainder of the cortex appears high. There are no adenomata and no signs of any hypertrophy. The medulla appears normal.

Thyroid: Essentially normal. There are extensive lymphoid infiltrations, but the glandular epithelium is low, and the colloid content high.

Hypophysis: The hypophysis may have been slightly enlarged. The great increase in basophile cells can be seen with the naked eye on the stained slide. There is a diffuse increase in this cell type throughout the whole gland, but more especially towards the periphery where they form dense masses almost suggesting adenomata. Many of them are vacuolated; others show globules of colloid in their cytoplasm. The eosinophiles are aggregated at the upper and lower poles of the gland. They tend to be large, but their number does not appear to be increased. As in Case 1 a large type of chromophobe is present, and once again this cell may contain basophile granules. A count of fifteen thousand cells from representative parts of the gland yielded a differential of 40 per cent eosinophiles, 35 per cent basophiles, and 25 per cent chromophobes. The pars intermedia shows a few colloid cysts. There is quite a marked invasion of the posterior lobe with basophiles. (These were not included in the cell count.)

Case 3. Autopsy 11913. Bilateral oöphorectomy 3 years previous to death. White female, aged 41 years.

Anatomical diagnosis: Peculiar chronic ulcerative lesions of vagina, uterus, bladder, and rectum; pelvic peritonitis; pyelonephritis; pyloric ulcers; haemangioma of liver; arteriosclerosis; absence of ovaries, tubes and appendix.

Microscopic examination: Adrenals: These are not enlarged. The zona glomerulosa is distinct. There are no adenomata. The medulla shows no recognisable lesions.

Thyroid: The epithelium is low and the acini filled with colloid. There are no lymphoid infiltrations.

Parathyroids: One of these is rather large, but section reveals no adenoma, the gland being composed of chief cells with a few scattered islands of eosinophiles.

Hypophysis: From the sections it would not appear that the gland had been enlarged. In the lateral lobes the eosinophiles predominate, but as the sections get nearer the central portion, these cells are replaced by a great increase in basophiles. These tend to form long columns running almost from the posterior lobe to the anterior margin of the gland. Many of these cells are vacuolated. The chromophobes are numerous and once again they appear to be of two types. The large type is found mainly among the islands of basophiles. The pars intermedia contains abundant colloid. There is no invasion of the pars nervosa.

Case 4. Autopsy 7668. White, female, aged 58 yrs. Bilateral oöphorectomy 6 years before death.

Anatomical diagnosis: Secondary carcinoma in brain, lung, bronchial and mediastinal lymph nodes; possibly primary in the lung; cholelithiasis; arteriosclerosis; congenital cysts in kidney; absence of uterus, tubes and ovaries.

Microscopical examination: Thyroid: The acini are lined with a flat epithelium. They are filled with colloid. The stroma is normal.

Adrenals: These are of normal size; the cortex is filled with fat. There are no adenomata. The medulla appears normal.

Hypophysis: The gland does not appear to have been enlarged. The periphery is occupied by dense aggregations of basophile cells which are increased in number. The eosinophiles do not seem to be diminished. The chromophobe cells show the variations noted in the previous cases. In this gland those of the large type are strikingly numerous. The basophiles are vacuolated, and it is of interest that these large chromophobe cells show in some cases a similar type of vacuolation. The vacuolisation of the basophile is usually quite distinctive, the vacuoles being larger and more sharply delimited than those found in the other cells.

There is little invasion of the posterior lobe.

DISCUSSION

While the series is lamentably small, the histological findings are sufficiently uniform to support the inference that castration in man does result in a certain type of reaction in the hypophysis. The most marked change, present in all four of the cases, was an increase in the number of the basophiles in the anterior lobe. In two of the cases there was an invasion of the posterior lobe by basophilic cells, but no significance can so far be attached to this, as it is present in many hypophyses. In cases 1 and 2 the eosinophiles would seem to be increased in diameter and not decreased, while in case 4 they are normal. It would appear, therefore, that any change in the eosinophiles, if connected at all with castration, is at least a variable one. The chromophobe cells are divisible into two types—a large and a small. The large type equals the chromophile cells in size, has a copious cytoplasm, and some of them show basophile granules. A study of these cells suggests that the mother cell of the basophile is the chromophobe, and that the large cell found in these glands is but a stage in the transition. Similar transition forms have been noticed in a non-castrate gland with extensive invasion of the pars nervosa by both basophiles and similar large chromophobe cells. If the inter-

pretation of these observations is correct, they constitute some basis for the belief in the existence of the basophile cell as such, and not merely as a stage in the life-history of the eosinophile cell as maintained by Collin (13).

While the presence of vacuoles in the basophiles has long been known, it has generally been accepted as a sign of degeneration. Fatty degeneration of these cells is difficult to reconcile with their proliferation, and the presence of vacuoles in the large chromophobe cells, which may be presumed to be young basophiles, would tend to indicate that these vacuoles may represent a storage of hormone. While fat stains of the gland generally reveal a surprising amount of fat especially in the chromophobes, these vacuoles show a rim of fat droplets, but the main body of the vacuole remains unstained.

These findings are so evidently at variance with those of Kon and Rössle that their papers were re-consulted. It was found that Kon used Schmidt's staining method, which it is now recognised stains the acidophile alpha granules with the basic dye. As he himself was unconscious of the reversal in the usual histological findings, his description stands as a verification of the basophilism of the human castrate hypophysis. Bailey (14) has already pointed out this error of Kon's in regard to report of a basophile adenoma in acromegaly. Rössle, on the other hand, was content to stain with haematoxylin and eosin which at best gives a poor differentiation. His pictures, moreover, show that he evidently mistook basophiles for eosinophiles—the cells depicted showing the vacuolation typical of the basophile. His heterotopic formation of eosinophiles in the periphery of the gland would seem to be none other than the proliferation of basophiles in their usual site. Kolde also stained with haematoxylin and eosin.

While the morphological changes offer evidence of an hypophyseal relationship, the main interest in such an investigation is physiological. Peirson (15) has recently reported the case of a man castrated three years previously. On injecting his urine into infant rats a positive Prolan A reaction was obtained. Zondek (16) has also shown that this substance is found in the urine of castrated women ten days after castration and for at least nine months after operation. Hence, following castration, a substance is secreted by the anterior lobe of the hypophysis which gives the same reaction as the Prolan A of the

urine of pregnant women. Furthermore, it has also been shown that the hypophysis of the castrated human being is richer in gonadotropic hormone than the normal. The histological findings, therefore, afford evidence of a morphological change indicative not only of an increase in secreted hormone, but also of stored hormone. In the castrated rat which also reacts to castration by the formation of basophile cells which finally become vacuolated, a similar storage of hormone is reported. The stored hormone seems to be mainly the luteinising factor, Prolan B. It is possible therefore that the changes in the basophiles are the morphological evidence of the increased manufacture and storage of this hormone.

In a recent study Phillips (17) showed that the hypophysis of the human foetus gave a slight stimulation of follicle formation. Such glands contain no basophiles. Similar results were obtained following the implantation of hypophyses from newly born infants. The follicle stimulating substance gradually increased as the child grew older. When, however, adult human hypophyses are implanted, there is found not only follicular stimulation but also luteinisation, a finding which supports the suggestion that the basophiles are possibly concerned in the manufacture of the luteinising hormone.

Koch, in his analysis of *Skoptzis*, describes four types:

1. The ordinary type with long extremities,
2. The type showing gigantism,
3. The type showing acromegaly,
4. The type with hypophyseal adiposity.

These changes would seem to indicate a varying response on the part of the cells producing growth hormone, and with this idea the inconstant changes in the eosinophile cells are in agreement.

In conclusion it is important to point out that while the above interpretation agrees with existing theories as regards the function of the anterior hypophysis, so little is known of the histological criteria of secretory activity of these cells that it can only be taken as one possible interpretation. Until more is learnt of the histological changes occurring in this gland from lesions in the other endocrine glands, it would be foolish to attempt to diagnose hyper- or hypogonadism from the number and nature of the basophiles of the anterior hypophysis.

SUMMARY

A. The hypophyses of 4 castrated human beings are described.

B. The changes found histologically are:

1. A marked increase in basophiles;
2. The appearance of large chromophobe cells with stages of transition between these and basophiles.
3. A varying response on the part of the eosinophile cells.
4. Vacuolisation and colloid formation in the basophile cells.

C. The possible physiological significance of these changes is discussed.

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ACTINOMYCOSIS GRAMINIS

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In 1890 Bostroem (1) described a filamentous organism as the cause of actinomycosis in cattle and man. After making some five hundred cultures he succeeded in growing an aërobic fungus which has subsubsequently been identified as Actinomyces graminis. Somewhat earlier Wolff and Israel (2) described an anaërobic strain which is now generally accepted as the aetiological agent in human and in bovine actinomycosis. Bostroem's organism, which resembles and is probably identical with the saprophytic fungi found in soil and on grasses, is occasionally found in lesions in man. Since its original description cases infected with this organism have appeared in the literature as pseudo-tuberculosis, streptothricosis, pseudo-actinomycosis, discomycosis, and agranular bronchonocardiosis, whilst many investigators have failed to distinguish between this strain and another aërobic but acid-fast strain—Actinomyces asteroides. MacCallum (3) has already pointed out that the term streptothrix is indefensible for this group of fungi, and that the name 'actinomyces' antedates the other variations in nomenclature. More recently the aërobic, non-acid-fast strain has been classified by Topley and Wilson (4) as Actinomyces graminis.

As the usual teaching is that only the acid-fast forms of the group are pathogenic for man, the following case was considered worthy of report.

The patient was a coloured female aged 35 years. She was employed in the city of Baltimore, Maryland, and had never worked in the country. In November, 1931, she had a hysterectomy performed for fibromyomata and subsequently developed a cough which persisted until her readmission to the hospital on January 13, 1932. Two weeks before admission she developed a painful swelling on the lateral aspect of the left thigh. One week later this was followed by the appearance of swelling on the median aspect of this thigh and in the right ante-

cubital fossa. At the same time she began to complain of fever and night-sweats. On admission her temperature was 103°F., her pulse rate 128, and her blood-pressure 120/70. The swellings on her left leg were compressed and subsequently incised with the discharge of a quantity of purulent material. X-ray plates of her chest were variously interpreted as pulmonary infarct, pneumonia, and finally as some non-tuberculous infection.

The Wassermann was strongly positive.

The blood showed total white cells 19,000, with a normal differential count. During her stay in the hospital the haemoglobin fell from 80 to 53 per cent.

The urine was normal.

Culture of the pus obtained from the abscess in the leg furnished a growth of an aërobic filamentous organism which was identified as a streptothrix. The patient was accordingly given potassium iodide by mouth and ethyl iodide by inhalation, but without any marked effect on the course of the disease. Her course continued downhill with the formation of new abscesses extending to both lungs, and she died on March 13th, two months after her admission.

An autopsy was performed eight hours after death. The following extracts from the report give the essential details.

Autopsy 12487. The body is that of an emaciated coloured female. On the external surface of the left thigh is a large ulcer measuring 8 x 4 cm., the base of which is covered with a yellowish-white slough. The pus is thin, and no sulphur granules can be seen. Similar ulcers are present on the median aspect of the left thigh and in the right ante-cubital fossa. These ulcers lie in the subcutaneous tissue extending to but not through the deep fascia. The underlying muscle and bone are normal.

The nose, mouths, and ears are normal.

The abdominal cavity contains no free fluid. The uterus has been removed and the site of operation appears normal save for a few adhesions.

Heart: The heart weighs 300 gm. It is soft and flabby and appears slightly enlarged. The epicardium is smooth. The endocardium is thin and the valves are delicate. Ventricles somewhat dilated. The myocardium shows no lesions.

Lungs: The pleura covering the left lung shows several recent adhesions. Over the posterior portion of the lung the visceral and parietal layers are densely adherent. Opaque yellowish masses project under the pleura over the anterior portion. The posterior part is completely replaced by a large greyish-white mass which measures 15 x 10 x 5 cm. This mass is soft and friable, and does not possess the fibrotic sponge-like character of the usual actinomycotic lesions. No sulphur granules are seen. On section the anterior part of the lung is studded throughout with opaque yellowish masses varying in size from 1 to 10 mm. in diameter, which have a tendency to become confluent. Between these masses the lung tissue is oedematous. The bronchi appear normal. The bronchial glands are not enlarged and on section show no lesions.

The pleura covering the right lung shows a small patch of fibrinous exudate

and several recent adhesions. The lung tissue is studded with small yellow opaque nodules similar to those in the left lung. There is no gross involvement of the bronchi or hilum lymph nodes.

Spleen: The spleen weighs 250 gm., and measures 13 x 10 x 5 cm. Its capsule is smooth and thin except at the lower pole where there is a small patch of fibrinous exudate. The Malpighian bodies are distinct. The pulp is dark red. Scattered throughout are several yellow opaque nodules resembling those in the lung. One of these lies just below the area of the capsule.

Liver: The liver weighs 1900 gm. and measures 26 x 21 x 8 cm. The capsule is thin. The bile-ducts and portal veins are normal. On section the lobules are sharply outlined. There is some congestion of the central areas and slight pallor of the peripheral zone. One small yellow nodule is found.

Kidneys: Each kidney weighs 200 gm., and measures 13 x 7 x 4 cm. The capsule is thin and strips readily, leaving a pale, homogeneous surface. The cortex is of normal width. The cortical striae are regular. In the left kidney several small yellowish nodules, 1 to 2 mm. in diameter, are found. The right kidney shows one large nodule, 5 mm. in diameter, in the cortex. The pelves, ureters and bladder show no lesions.

Nothing abnormal is found in the cervical stump of the uterus.

The tongue, tonsils, mandible, neck organs, retroperitoneal tissue, ovaries, adrenals, intestines, and mesenteric glands show no lesions.

Unfortunately, the cranial cavity could not be examined.

Smears made from the ulcers, lungs, and renal lesions show the presence of a branching mycelium, which is Gram-positive, but not acid-fast. Cultures were made from the heart's blood, lungs, and ulcers.

Microscopic examination

Lungs. The section from the large mass in the left lung shows complete disorganisation of the pulmonary tissue. It is found to be composed of necrotic débris infiltrated by neutrophiles, lymphocytes and large mononuclears. Many of the infiltrating cells show pyknosis and fragmentation of their nuclei. The blood-vessels are thrombosed. There is no excess of fibrous tissue even at the margin of the lesion, the necrotic area fading gradually into areas in which the lung alveoli are filled with fibrin and neutrophiles. The remainder of the lung shows many small nodular areas of infiltration. The centre of each of these is composed of pink-staining, necrotic tissue and nuclear débris. Surrounding this is a zone of cellular infiltration, the infiltrating cells being the same as those in the larger mass. There are no giant cells. Around this the lung alveoli are compressed and filled with fibrin. Other areas of lung show a still earlier state of the infective process, the alveoli showing a pneumonic consolidation in which it is possible to demonstrate the organism. The intervening alveoli are oedematous. A large bronchus contains a mass of necrotic material in which the organism is present, and this may represent the path by which the infection became generalised throughout the lungs.

Histologically, the nodules in the right lung, spleen and kidneys are similar to those just described. Everywhere the lesion is characterised by coagulation necrosis, infiltration by neutrophiles, lymphocytes, and mononuclears and the absence of giant cells and *Drüsen* forms.

Bacterial stains show the presence of a dense network of a mycelium. This is Gram-positive but non-acid-fast. It grows in chains which show true branching. The organism has a granular appearance reminiscent of B. diphtheriae, but no spore formation is evident. No *Drüsen* forms, such as are regarded as characteristic in infection by Actinomyces bovis are present, though the mycelium is found in dense radiating masses.

Anatomical diagnosis: Generalised actinomycosis; primary abscess, left lung; secondary involvement of both lungs, liver, spleen, kidneys and subcutaneous tissue of left thigh and right arm.

Cultures: The organism was found to grow aërobically in broth, Sabouraud's medium or on agar. There was no growth under strictly anaërobic conditions. It grows well at room temperature and some cultures have been kept alive for six months. Old cultures on potato show the formation of a yellowish pigment. This turns litmus alkaline in milk in four to five days. It liquefies gelatine. Examination of the organism on all of the media shows that it is extremely pleomorphic. Coccoid, bacillary, long branching forms, and dense masses of radiating filaments of the mycelium, are common. No formation of clubs was noticed.

There is no haemolysis on blood agar.

The organism is non-motile and non-sporing.

All forms are Gram-positive but non-acid-fast.

These are the characteristics of the organism classified by Topley and Wilson (4) as Actinomyces graminis.

Pathogenicity: It is stated by Topley and Wilson (4) that the organism is non-pathogenic for laboratory animals, and Magnusson (5) in a recent review writes that no one has yet succeeded in producing even an abscess by its injection, and is inclined to consider it a harmless saphrophyte. Certain it is that in many of the cases in which it has been found in old cavities in the lung it is merely a contaminant and has played no part in the pathogenesis of the lesion.

Cultures were injected subcutaneously, intravenously, intraperitoneally, and intrapleurally into rabbits, guinea-pigs, rats and mice. In no instance did the animal die, though some were allowed to live

three months following the injections. Animals were killed 24 hours, 48 hours, 5 days, 12 days and 4 to 12 weeks after being injected. As the nature of the lesions produced was similar in all, one description will suffice.

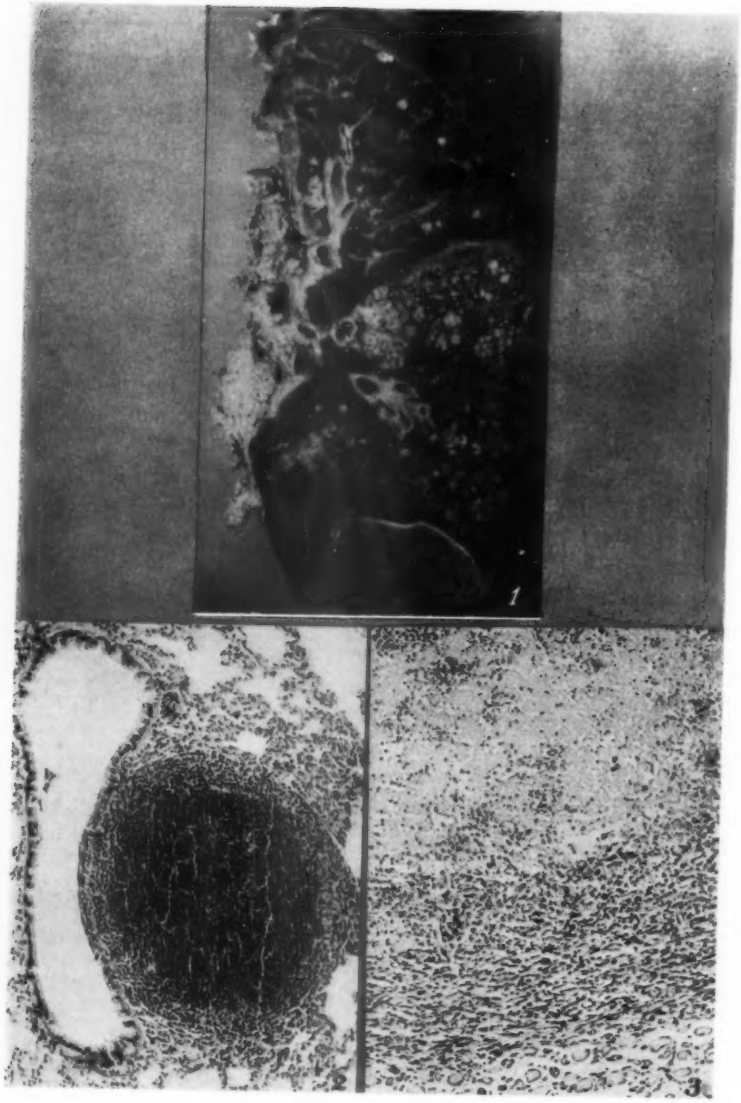
Following intravenous injection the lungs show many small nodules which are just evident to the naked eye in 24 hours. These nodules are whitish and somewhat gelatinous in appearance. Microscopically, they are found to be dense aggregations of neutrophile leucocytes. In the centre of each is a capillary distended with these cells. The organism was recovered from these nodules on culture, though on staining the sections for bacteria one is impressed by the difficulty in demonstrating it, prolonged search being necessary before one or two branching filaments are found.

In 48 hours the lesion is similar macroscopically. Microscopically, the neutrophile infiltration is now surrounded by a zone of lymphoid and large mononuclear cells.

In five days the lesions have not progressed in size. The centre of each nodule is composed of giant cells which are strikingly numerous. Around these are the collections of neutrophiles, lymphocytes, and mononuclears. There is no massive necrosis, though the individual cells show pyknosis and fragmentation of their nuclei. A few nodules were demonstrable in the livers of two rabbits, but this was an unusual finding since most the mycelial fragments are apparently filtered out by the capillary bed of the lung. The liver nodules always show a large central zone of necrosis.

In twelve days there is a well marked fibroblastic reaction at the periphery of the nodules. These have laid down collagen, and the lesion is evidently in process of being walled off. There is little change in its histological characteristics.

Intraperitoneal injections produce scattered nodules over the peritoneal surfaces in the rabbit, mouse and guinea-pig. In the rat the reaction is less marked, the injection merely producing a slight fibrinous exudate around clumps of the organism which soon disappears. In the reacting animals the nodules are small and are quickly encapsulated. In animals allowed to live six weeks, one or two nodules up to 1 cm. in diameter may be found. Microscopically, these are similar to the lesions already described. In rabbits and mice these lesions



FIGS. 1 TO 3

contain deposits of calcium. Intrapleural injections produce similar localised lesions. Subcutaneous injections produce a localised abscess in mice, guinea-pigs, rats and rabbits. The histology in no way differs from that already described.

No *Drüsen* forms were found in any of the lesions. The organisms were no more numerous in the long-standing than in the twenty-four hour lesions.

COMMENTARY

It would appear that the organism responsible for the lesions producing death in this patient was *actinomyces graminis*. The lesions produced in animals, while they did not lead to death, were of similar nature and histology.

The resemblance of the lesions to those produced by *B. tuberculosis*—the central zone of coagulation necrosis, the surrounding zones of lymphoid and mononuclear infiltration—is at first striking, but they can be readily differentiated by the well marked neutrophile reaction in those produced by the fungus. From the number of neutrophile leucocytes present in the infiltrations it might be expected that their death would lead to the liberation of their proteolytic enzymes and subsequent liquefaction. Yet, in the case described, the result was a coagulation necrosis, and similar lesions were found in some of the experimental animals. No satisfactory explanation for this rather peculiar reaction has been found.

FIGS. 1 TO 3

FIG. 1. Section through the lung substance to show the lesions produced by dissemination of the organism. The general resemblance to a tuberculous process is worthy of note. The hilum lymph nodes are markedly anthracotic but show no lesions. (Photographs by Mr. Milton Kougl.)

FIG. 2. The lung of a rabbit, 24 hours after the intravenous injection of broth culture, showing the inflammatory reaction in the neighborhood of a bronchiole. The infiltrating cells at this stage are chiefly polymorphonuclears, with some large mononuclears in the peripheral zone of the lesion.

FIG. 3. The edge of a nodule in the parietal peritoneum of a rabbit 4 weeks after intraperitoneal injection of a broth culture. It is surrounded by a capsule of fibrous tissue. The centre consists of a caseous material in which are some polymorphonuclears and necrotic cells.

It is worthy of note that just as in patients and animals infected by Actinomyces bovis there is in this case no involvement of the lymph nodes.

No club or *Drüsen* formation was found in any of the lesions, and in this respect the organism differs from Actinomyces bovis and Actinomyces asteroides. Many cases of infection by the asteroides strain, however, are similar in this respect, though on injection into animals these strains may produce the typical granules (MacCallum).

Granule formation has, perhaps, been unduly emphasised as a characteristic of actinomycotic infections, for it has been shown that it is not confined to this group of organisms. Nicaud (6) has recently described similar granules "*en forme d'étoiles à branches courtes*" in the experimental lesions produced by Aspergillus fumigatus, and similar bodies have been described in Sporotrichosis (Pinoy (7)) and Moniliasis (Magrou (8)). Granule formation has also been found in some bacterial infections and Lignières and Spitz (9), in describing a form of pseudo-actinomycosis due to a Gram-negative bacillus, the Actinobacillus, make the suggestion that all such organisms be grouped under the name of actinophytes. These observations are sufficient to show that the presence or absence of granules, although suggestive, is not in itself sufficient to establish or negative the diagnosis of actinomycosis, and that, as with other bacterial diseases, the criteria of infection are the isolation and culture of the fungus.

Whilst the aërobic strains of actinomyces have been frequently found in nature, the anaërobic types have not been found outside the animal body. Naslund (10), while claiming that the anaërobic type can be found in the mouths of human beings, states that Bostroem's strain is rare in this situation. Whatever may be the mode of infection with the Wolff-Israel strain, the probability is that infection with the aërobic strain is exogenous. It corresponds to many of the fungi found in nature, in earth and on plants; it grows luxuriantly at 18° to 22°C., and is aërobic. It not infrequently produces the primary lesion in the lungs (see cases of Jamison (11), Foulerton and Jones (12), Holmes (13), and others) so that the disease is described by Castellani (14) as agranular bronchonocardiosis.

The non-progressive nature of the lesions in the experimental animals points to a high degree of resistance against the disease in

these animals. The case reported, however, is characterised by the rapidly progressive nature of the infection, and the absence of fibroblastic reaction. Naslund in his recent work concludes that the disease due to the aërobic form—Actinomyces asteroides—in human beings is more malignant than that produced by the anaërobic form. The present case seems to indicate that this statement probably holds true also for the much rarer infection by Actinomyces graminis.

SUMMARY

1. A case of primary actinomycosis of the lung, with haematogenous infection of the spleen, liver, kidneys and subcutaneous tissue is described.

2. The fungus is aërobic, Gram-positive, and non-acid-fast, and was identified as Actinomyces graminis (Bostroem).

3. The organism produces lesions in guinea-pigs, rabbits, and mice, but these are non-progressive and soon heal.

4. No *Drüsen* forms were found either in the tissues of the patient or in the infected animals.

I wish to acknowledge my indebtedness to Professor W. G. MacCallum for permission to publish this case, and to Mrs. I. G. Schaub for much help with the bacteriological investigations.

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EXPERIMENTAL YAWS[1]

II. Comparison of the Infection with Experimental Syphilis

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In the preceding paper of this series (1), the isolation of a number of strains of *T. pertenue* from cases of yaws in Haiti, together with the isolation in the same country of a single strain of *T. pallidum* from a patient with syphilis, was described. As pointed out in that communication, the purpose of the investigation was to obtain spirochetes from cases of yaws and also from cases of syphilis, encountered *in the same locality*, and to observe the behavior of these organisms in animals with a view to determining whether or not experimental yaws differed from experimental syphilis when both diseases were artificially produced by infection with organisms coming from the same part of the world. Previous workers have already described experimental yaws and have compared it with experimental syphilis, but, so far as we are aware, such comparisons have not dealt with strains of yaws treponemes and syphilis treponemes isolated in the same tropical community. It is obvious that such a comparison might well throw light upon the much discussed question of the identity or non-identity of the two diseases, yaws and syphilis.

In 1910 Nichols (2) isolated a strain of treponemes from a negro soldier returning from the Philippines. The subsequent course of the disease in this patient was such as to lead Nichols later to question the original diagnosis of yaws and, in consequence, the experimental work done with this strain must be disregarded. In studying a strain of *T. pertenue* obtained from an American soldier presumably infected in France, Schamberg (3), after observing the experimental disease

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in 4 generations of rabbits, states "There is essentially no difference in the experimental testicular lesion of syphilis and yaws."

In 1927 Pearce and Brown (4) first described in detail the characteristics of infections produced in rabbits by two different strains of yaws treponemes. One of these was obtained from a patient in New York who had contracted yaws in Montserrat, B. W. I.; the other was isolated in Panama by Nichols. The more striking features which they noted were (1) a peculiar granular periorchitis quite unlike the testicular lesion observed in experimental syphilis, (2) relative infrequency of clinically recognizable involvement of the uninoculated testis, and (3) total absence of generalized lesions. Nichols (5), working with yaws virus obtained originally in Panama, noted the frequent occurrence of this granular periorchitis, as did Matsumoto and his associates (6, 7) employing strains from the South Sea Islands. The last named workers observed generalized lesions of the skin, bones and eyes in about 10 per cent of rabbits following intratesticular inoculation.

Jahnel and Lang (8) found that the experimental disease produced by a strain of *T. pertenue* from Sumatra differed in certain respects from that caused by other strains of yaws virus, as well as from that produced by several strains of *T. pallidum*. Typical granular periorchitis was not noted, but neither was it observed by them in animals inoculated with strains (referred to above) obtained from Nichols and from Pearce and Brown. Kakishita (9), working with a strain of yaws treponemes secured from Schobl in the Philippines, noted the typical granular periorchitis in some instances, although the testicular lesions could not uniformly be distinguished from those produced by *T. pallidum*; no generalized lesions were observed by him over a period of 2 years.

From the literature, therefore, it would appear that granular orchitis or periorchitis has been observed at one time or another in animals inoculated with strains from the West Indies, Central America, the Philippines, and the South Sea Islands, and when present is conceded to be characteristic of yaws, although the frequency with which it occurs seems to vary considerably. With the exception of Schamberg, each author conveys the impression that even in the absence of the characteristic periorchitis yaws lesions still present more or less con-

stant, if less well defined, differences from those of syphilis. All of these writers comment upon the relative difficulty of propagating strains of *Treponema pertenue* as compared with strains of *Treponema pallidum*, and that has, also, been our experience.

EXPERIMENTAL

Eight strains of yaws treponemes were recovered in the winter of 1929–1930 from as many patients living in widely separated districts of Haiti, the source in each instance being a native negro exhibiting characteristic lesions of the disease. At the same time, a strain of *T. pallidum* was isolated from a native negro who presented a typical Hunterian penile chancre. The details concerning the source of each strain and mode of isolation were recorded in the previous communication (1). The animals infected with these organisms were transported to Baltimore and all further observations were made there.

The animals included in this study are mainly those which were used in propagating the respective strains, and all the common laboratory breeds of rabbits were represented. Comparison will be made only between rabbits inoculated with material in which actively motile *Treponema pertenue* or *Treponema pallidum* was demonstrated by dark field examination. In the transfer of virus from rabbit to rabbit a technique similar to that commonly employed in experimental syphilis was used, and was exactly the same for both the yaws and syphilis strains. Small portions of an affected testis were emulsified in normal saline solution and 0.2–0.3 cc. were injected into one or both testes of normal adult rabbits. Transfers were made usually at intervals of 4–8 weeks, an effort being made to prepare the inoculum from actively progressing lesions. The test animals for both yaws and syphilis were kept under identical conditions as regards caging, bedding, feeding, temperature of the room, etc.

Of the eight yaws strains isolated in Haiti, five were subsequently discarded for reasons of economy, and two of the remaining three were lost in the 6th animal passage. During the period that all eight strains were observed, however, it was evident that the disease picture produced in rabbits by each strain was essentially the same. The surviving strain, designated "Y 9," has now passed through 15 generations of rabbits; among a total of 135 animals available for study 78 were

inoculated with Strain Y 9, and 57 with one of the yaws strains subsequently discarded or lost.

For comparison with the above there are available the records of 46 animals infected with the Haiti strain of syphilis, hereinafter designated "Strain K." This strain has now passed through 20 generations of rabbits. An additional basis of comparison is afforded by 6 stock strains of syphilis virus which have been carried in this laboratory for approximately ten years, one strain having been isolated in Europe and the others in the United States.

RESULTS

In comparing the course, in rabbits, of the two infections, experimental syphilis and experimental yaws, we shall focus our attention on the following points: (1) incubation period; (2) the initial lesion after (a) intratesticular and (b) intracutaneous inoculation; (3) metastatic lesions; (4) seasonal variation.

1. The incubation period

The lapse of time from inoculation to the first appearance of clinically recognizable changes in the testis was on the average definitely longer among yaws rabbits than among those inoculated with syphilis. In the former the incubation period varied from a minimum of 20 days to a maximum of 108 days, while 12 and 65 days represented the minimum and maximum, respectively, among "Strain K" animals. The difference is even more strikingly shown in Table I for it will be seen that approximately 64 per cent of the latter developed an initial lesion within 30 days after inoculation, while among the yaws rabbits only 20 per cent exhibited lesions within this period. The average incubation period following intratesticular inoculation was, in the yaws animals, 38.6 days, and, in the "Strain K" rabbits, 28.7 days.

2a. The initial lesion in the testis

The reaction in the rabbit's testis following inoculation of that organ with yaws virus presents characteristics which enable one to differentiate between this disease and experimental syphilis in the vast majority of instances. The essential feature of the yaws testicular lesion consists of scattered miliary granules in the body of the testis, the

tunic, or the epididymis. The testis at first feels finely granular, as though small grains of sand were within its substance or upon its surface. Commonly within a week or two the granules become larger and more definite, but while the testis at that time may be a little larger than normal and somewhat firm, it almost never approximates the tremendous enlargement or the marked induration which is so commonly a feature of the lesion produced by *T. pallidum*. Edema of the scrotum has not once been observed by us.

Upon exposure, small white or gray granules 1 mm. or less in diameter and varying in number can be seen distributed over the surface of the testis and, often, of the epididymis. The tunic alone may be involved but most often, as shown by microscopic section, miliary lesions are situated also just under the tunic and within the body of the

TABLE I

Incubation period—intratesticular inoculation

INCUBATION PERIOD	YAWS	SYPHILIS
days	*per cent*	*per cent*
Less than 20 days	0	20.0
20–29	20.8	44.4
30–39	43.5	13.3
40–49	22.7	15.2
50+	12.9	7.0

testis. Not infrequently the testis feels granular on palpation and shows minute lesions on microscopic examination, and yet appears perfectly normal to the naked eye.

Histologically the miliary lesions are quite similar, whether located in the tunic, in the subserous tissue, or in the body of the testis, and consist of localized collections of large and small lymphocytes. Lesions in the body of the testis usually begin in the interstitial tissue and do not often involve the seminiferous tubules. Eosinophile cells are frequently seen in great numbers along with the lymphocytes, but the occurrence of these cells in yaws lesions in rabbits is probably not of special significance.

Enlargement of the head of the epididymis is one of the most constant features, and may occur alone or in association with a granular

orchitis or periorchitis. The epididymal lesion is usually firm but rarely, if ever, so markedly indurated as in syphilis. There were instances in which the epididymis was the only site where lesions developed, although the virus itself was deposited in the body of the testis.

Testicular lesions somewhat different from those described above have been observed by us occasionally. Thus a few firm nodules 1–3 mm. in diameter may develop in the body of the testis. Again, a solitary indurated nodule may appear in the tunic or subscrotal tissue, and infrequently tiny nodules will develop in the tail of the epididymis. A relatively large number of animals show only insignificant lesions in the testis and considerable experience is often required in order to detect by palpation the slight changes that occur. Many of these clinically doubtful lesions have been proved to be yaws by histological examination or by darkfield study of the tissues.

The duration of the initial yaws lesions varies from a few days to several months. Commonly the changes become more marked during the first few weeks after the onset; then they gradually retrogress during the succeeding 4–8 weeks, leaving the testis essentially normal or atrophic. During the period of activity *T. pertenue* can be demonstrated in material obtained by aspiration or by emulsification of portions of the affected tissue.

The characteristic granular periorchitis described above has been observed among rabbits inoculated intratesticularly with each of the 8 yaws strains. It has also been observed after intravenous inoculation. As far as we can determine there has been no essential change in the character of the experimental infection with the passage of time.

The lesions produced in the rabbit's testis by the Haiti strain of syphilis (Strain K) differ strikingly from those described above for yaws, and conform in general to the lesions resulting from the inoculation of rabbits with other strains of *T. pallidum*. The earliest sign of involvement is usually diffuse enlargement with induration of the entire testis, or the appearance of a solitary indurated nodule. Progression of the lesion is frequently rapid, with accompanying edema of the scrotum, and where the disease is fully developed the testis is enlarged, sometimes to twice its normal size and, in addition, is mark-

edly indurated. These characteristics were present in the first series of rabbits inoculated with this strain and have been constantly present in succeeding series. Moreover, the initial reaction in animals infected with "Strain K"was almost always well marked as contrasted with the large number of slight and equivocal lesions encountered in yaws. Thus, of 46 animals inoculated with "Strain K" only one failed to show unmistakable clinical signs of infection, while in 15.5 per cent of 135 animals inoculated with material containing actively motile *T. pertenue*, the clinical signs of infection were questionable, and in 9.6 per cent the testis showed no clinical signs at all.

A comparison in detail of the histological appearance of the experimental yaws and syphilis lesions will not be presented in this communication, but will be reserved for a future report.

We do not wish to give the impression that every rabbit in this series, inoculated intratesticularly with yaws virus, exhibited lesions that were distinct from all those that occur in animals inoculated with *T. pallidum*, for an occasional yaws rabbit will present a testicular nodule which, because of its size and induration, cannot be distinguished from nodules observed in experimental syphilis. These instances are the exception, however, and we have been struck by the differences in the character and evolution of the lesions caused by the two organisms in the vast majority of rabbits.

2b. The initial lesion after intracutaneous inoculation

Following intracutaneous inoculation of yaws virus in rabbits there appears, at the site of inoculation, usually during the second or third week, a small area of erythema. After a few days desquamation of fine scales occurs and the erythema begins to subside. Many lesions progress no further than this stage but in some the lesion becomes larger and assumes a very characteristic appearance. The affected area becomes darker in color and slightly raised but there is, however, no induration either of the lesion itself or in the surrounding tissue and the entire lesion remains quite superficial. Desquamation continues and the papillae of the skin become accentuated. If ulceration and crust formation occur, the lesion assumes a nutmeg-grater appearance. *T. pertenue* can be found in serum obtained from these cutaneous lesions.

Histological examination reveals that the projections noted macroscopically are due largely to localized collections of lymphocytes in the corium just beneath the epidermis. The overlying epidermal layer in some places is intact, while in others it is destroyed. Frequently there are collections of round cells deeper in the corium and about the base of hair follicles, but rarely does the lymphocytic infiltration extend beneath the corium. Perivascular infiltration occurs but is not a striking feature.

In contrast to the above, when virulent strains of *T. pallidum*, including "Strain K," are deposited in the skin of the rabbit there develops a raised, indurated, and button-like lesion which undergoes superficial necrosis, giving rise to a typical chancre. Histologically, this lesion shows tremendous infiltration of round cells and the normal architecture of the skin is entirely destroyed. Large areas of lymphocytic infiltration commonly extend well down into the subcutaneous tissue.

In the case of intracutaneous inoculation, then, the differences between the reactions produced by the organisms of yaws on the one hand and syphilis on the other are, if anything, more striking than after intratesticular inoculation.

3. Metastatic lesions

Scrotal lesions. In experimental syphilis, involvement of one or both scrota with the formation of a typical chancre is not an uncommon occurrence after intratesticular inoculation either as a result of direct extension of the disease process or as a result of metastasis. The same type of involvement occurs in yaws, but in this disease the scrotal lesion appears quite different from that seen in syphilis. In yaws the scrotal ulcer is small, measuring 5–10 mms., is very superficial, and is covered with a thin crust which, when removed, reveals a bright red slightly granular base with numerous bleeding points. *Treponema pertenue* is easily demonstrable in serum from this lesion. The total absence of induration about the base of the ulcer is a notable feature. In experimental syphilis, scrotal ulcers are commonly larger than in yaws, there is considerable induration about the base, and necrosis extends as a rule through the integument into the subscrotal tissue.

Involvement of the uninoculated testis. Metastasis of treponemata to the uninoculated testis occurs in both yaws and syphilis, the lesion in each case partaking of the characteristics of the respective disease and as a rule is not so extensive as the initial reaction. Metastatic lesions occurred far less often, however, in the yaws animals than in rabbits inoculated with Strain K. Thus among 68 yaws rabbits inoculated in one testis and observed for 90 days or longer, 6 or 8.8 per cent presented a definite lesion in the opposite testis, in 9 or 13.2 per cent there developed questionable lesions, while in 53, or 78 per cent, the uninoculated testis remained normal. In 3 animals metastatic lesions occurred in both the testis and scrotum. On the other hand, in 84.2 per cent of the Strain K rabbits metastatic lesions developed in the opposite testis, a figure corresponding closely with that noted in the other syphilis strains. The metastatic lesions in yaws appeared between the 70th and 100th day after inoculation, while in syphilis they tended to occur at an earlier date.

Generalized lesions. The proportion of syphilitic animals that exhibit generalized lesions may vary somewhat according to the strain of virus, but as far as we are aware all strains of syphilis treponemes that have been adequately studied may produce lesions of the bone and periosteum, the skin, and the eye, the type of lesion being essentially the same for all strains. In a total of 42 animals inoculated intratesticularly with "Strain K" and observed for a sufficiently long period of time, generalized lesions were observed in 11, or 26 per cent. Of these, multiple bone lesions occurred in 7, multiple skin lesions in 2, and keratitis of one or both eyes in 7. Generalized lesions were observed among the first animals inoculated as well as in later series. Among 87 yaws animals similarly studied not one exhibited lesions of the skin, bone or eyes. It is conceivable, of course, that some form of skin lesion may have developed which escaped detection, but certainly generalised lesions of the type commonly observed in experimental syphilis did not occur in our yaws animals. In this respect our experience is entirely in accord with that of Pearce and Brown (4). We were much impressed by the striking difference in the incidence of generalised lesions in the two groups of animals, and would not be surprised if further study would show that this difference is constant, and can be used to differentiate the two experimental infections.

Seasonal variation. The tendency of experimental syphilis in the rabbit to run a relatively benign course during the summer months is well known to investigators in this field. The same phenomenon was observed in yaws to an even greater degree, two of our strains having been lost during the summer period. Frequently animals inoculated with yaws virus containing actively motile organisms at the beginning of summer have shown no lesions until the onset of cool weather, and there was noted a marked tendency for initial lesions to be transient during the warmer months.

DISCUSSION

The foregoing results clearly show that treponemes from 8 different cases of yaws encountered in Haiti, when transferred to rabbits and propagated in these animals by successive transfers, were capable of producing an experimental disease which exhibited characteristic and constant clinical and pathological features. No differences were observed in the experimental infection produced by each of the 8 strains. The course of this experimental infection has been quite similar to that produced in rabbits by other investigators working with strains of treponemes obtained from yaws patients in other parts of the world. This experimental yaws infection has, in our hands, been found to differ markedly from experimental syphilis, not only as produced by strains of *T. pallidum* isolated in the temperate zone, but also, and this seems to us most significant, it has been found to differ from experimental syphilis produced by a strain of *T. pallidum* isolated in the *same* (tropical) region.

Thus it is possible to say that there existed in Haiti at the same time, two kinds of treponemes, one which produced yaws in human beings and also a characteristic disease picture in rabbits, and another which produced characteristic syphilis in the native population and, in rabbits, a disease picture which could be easily differentiated from that produced in these same animals by the yaws treponemes.

When one considers that the two experimental infections were observed concurrently in series of rabbits kept in the same animal quarters and under the same general conditions as regards diet, caging and bedding, so that the only variables were the strains of treponemes themselves, it is difficult to escape the conclusion that the differences

observed in the two experimental infections were to be ascribed to inherent differences in the strains of treponemes themselves. This conclusion, if true, lends support to the view that at the present time syphilis and yaws are different diseases, and that yaws is not just syphilis modified in some mysterious fashion by circumstances which operate in the tropics.

It is of course entirely possible that at some remote date in the past the treponemes of yaws and those of syphilis were identical, and that they produced only one type of disease, but of this there is no definite evidence at the present time. There also exists the possibility that the yaws strains of treponemes may in the course of time and as a result of animal passage change their characteristics in such a way that the disease produced by them in rabbits may become similar to that produced by strains of treponemes obtained from syphilis. As yet, we have not seen any evidence that that event is likely to happen.[2]

SUMMARY AND CONCLUSIONS

1. The experimental disease produced in rabbits by eight strains of *T. pertenue* isolated in Haiti is compared with that produced by (1) a strain of *T. pallidum* isolated in Haiti and by (2) several strains of *T. pallidum* isolated in the temperature zone.

2. No differences were noted in the experimental infection in rabbits inoculated with the eight strains of yaws virus.

3. The disease picture produced by the yaws virus presented striking and for the most part constant differences, from that produced by the Haiti strain of syphilis.

4. The Haiti strain of syphilis gave rise to an experimental disease

[2] After this paper had gone to press our attention was called to the statement by Manteufel in his article in the Handbuch der Haut- und Geschlechtskrankheiten, Band XVII/3, p. 364, to the effect that he had observed a gradual change in the character of experimental yaws lesions in rabbits as a result of continued passage of the yaws virus through these animals. The experimental yaws lesions changed in such a way that they took on the characteristics of syphilitic lesions and eventually, according to Manteufel, could scarcely be distinguished from such lesions. The original communication in which these observations were reported is not available to us at the present time and we are not able to offer any further comment upon them.

in rabbits which was similar in every way to that produced by several strains of syphilis virus isolated in the temperature zone.

5. The bearing of these observations upon the identity of syphilis and yaws is discussed.

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AN INVESTIGATION OF SOME EFFECTS OF PREGNANCY NOTED SIX WEEKS AND ONE YEAR AFTER DELIVERY

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In 1916, a "six weeks return" clinic was established by the Obstetrical Department of the Johns Hopkins Hospital. The purpose of this clinic was the reëxamination of patients delivered by the Department together with their children, at a period approximately coinciding with the end of the puerperium. The child was weighed, its feedings noted, and its skin, eyes, umbilicus and genitalia inspected. If any abnormality was found the child was at once referred to the Department of Pediatrics for treatment. The mother was questioned as to symptoms, and a careful pelvic examination made, with an attempt at correction of any abnormality. In 1919, three years after the foundation of the former, a "year return" clinic was begun, which the patient was encouraged to attend with her baby at a period from twelve to thirteen months after delivery. The purpose of this clinic was essentially that of the former, with the addition that it was attempted to estimate at this time what effect the pregnancy had had upon the health and general efficiency of the woman. Both of these clinics were established by and were for a long time under the direct supervision of the late Dr. J. W. Williams, Professor of Obstetrics. Several years ago, in order that the information acquired through these clinics might be put in easily available form, Dr. Williams caused the data accumulated on those patients making return visits, and delivered during the period January 10, 1919 to September 12, 1927, to be recorded on punch cards, but no analysis of this work was ever made by him. It has seemed to the author not only fitting but also of value to make such an analysis, particularly since the material at hand was believed to be of considerable importance by Dr. Williams and represents a large amount of work done by him and his associates.

The present paper, then, is a study of information on both mothers and children gained from the above coded punch cards, and includes items from examinations at the time of discharge of the patient from the hospital, six weeks, and twelve to thirteen months, respectively, after delivery.

GENERAL MAKE-UP OF THE SERIES

During the above period, comprising approximately eight and two-thirds years, 7163 women were delivered at or near term by the hospital service. Of these 2885, or 40.28 per cent, visited the "year return" clinic, and these cases form the basis for the following study. Moreover, 1334 of these latter patients also returned for examination six weeks after delivery (18.62 per cent of the total deliveries) and records obtained at this time are included in the analysis: 1028 of the women were white, comprising 35.63 per cent of the series and 32.06 per cent of the total whites delivered, while 1857 were black and make up 64.37 per cent of the series and 46.93 per cent of the total of that race delivered. Moreover, 45.33 per cent of the whites and 59.18 per cent of the blacks in the series were primiparae, the remainder being multiparae of various parities including an appreciable number of women of both races who had already borne ten or more children.

These above figures and percentages are included in order to illustrate the fact that the cases under study comprise a representative series in so far as the experience of the clinic is concerned. It should be noted, however, that the patients do not comprise a representative cross section of the child-bearing population as a whole, inasmuch as no private patients are included. The material at hand, both white and black, is made up of tenement dwellers from a large city and from the lowest strata of society. Moreover, in addition to those patients who had registered in the dispensary during pregnancy and had received a varying amount of prenatal care, there are a relatively large number who were first seen during labor as referred emergency cases and hence showed an abnormally high percentage of obstetric abnormalities.

STATISTICS OF INFANTS

Among the infants born to the 2885 patients in the series were 37 instances of twins and one of triplets, giving a total of 2924. The

incidence of twins, then, was 1 in 78 deliveries, or slightly greater than is usually observed for the population at large.

Table 1 shows in detail the foetal and infant mortality for the series, divided according to the race of the mother. It will be noted that all the rates given are higher in the black than in the white race. Such has been our constant experience whenever statistics on infants are collected at the clinic and the increased frequency of syphilis in the black race only partially accounts for it. Moreover, we have previously demonstrated that the high incidence of contracted pelvis among the blacks as contrasted with the whites is not responsible for the observed difference in stillborn mortality between the two races. It is our

TABLE 1

Gross infant mortality rate (per cent of total delivered)

	WHITE	BLACK	TOTAL
	per cent	*per cent*	*per cent*
Stillborn	4.43	6.47	5.75
Died in hospital	2.60	3.08	2.91
Died 1–3 months	1.16	1.48	1.37
Died 4–6 months	1.06	1.38	1.26
Died 7–9 months	0.67	1.27	1.06
Died 10–12 months	0.87	0.80	0.82
Died, time unknown	0.00	0.16	0.10
Unknown	0.19	0.16	0.17
Alive at 1 year	89.02	85.21	86.56

opinion that some definite racial difference is responsible for the disparity observed. We realize that the mortality figures portrayed here are higher than those usually quoted for the community at large, but it would seem probable that the explanation lies in the low social condition of the patients of the series, making for mothers definitely below par physically and children whose care during the hazardous first year of life is inadequate.

Table 2 gives the examiner's clinical impression as to the health of the children remaining alive at the end of one year. It will be noted that between 90 and 95 per cent of the infants of both races are classified as being in excellent or good condition. This is a surprisingly high figure for a series of tenement children, and the reason for it

would seem to lie in the efficient supervision given by the various private and municipal child welfare organizations to whom the patients are referred at the time of discharge from the hospital.

The type of feeding employed for the children at the time of discharge of the mother from the hospital is shown in table 3. It might be stated that the average ward patient is sent home from nine to fourteen days after delivery, and usually nearer the former than the latter time. Less than one per cent of the entire group was on complete artificial feeding at this time, and for this various conditions in the

TABLE 2

Condition of living children at 1 year (per cent of total living)

	WHITE	BLACK	TOTAL
	per cent	*per cent*	*per cent*
Excellent	82.41	79.03	80.26
Good	13.36	14.05	13.80
Fair	3.12	4.55	4.03
Poor	1.11	2.37	1.91

TABLE 3

Feeding of children at time of discharge from hospital (per cent of total discharged)

	PRIMIPARAE			MULTIPARAE		
	White	Black	Total	White	Black	Total
	per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
Maternal	57.44	69.44	65.81	63.04	70.09	67.03
Mixed	41.88	29.97	33.56	35.80	29.17	32.04
Artificial	0.69	0.59	0.62	1.17	0.74	0.93

mother contraindicating nursing were usually responsible. A study of this table would seem to indicate that the average black woman, whether primipara or multipara, produces earlier in the puerperium a supply of breast milk adequate for the child's needs than does the white. Approximately one-third of the children in the series needed supplementary feedings of cow's milk during the second week after delivery.

Table 4 indicates the type of feedings at a period approximately six weeks after delivery and demonstrates several points of interest. In

the first place, although the percentage of black babies at this time on artificial feeding was very little higher than on their discharge from the hospital, there was a marked increase in the whites, so that approximately one-sixth of those children born to primiparae and one-tenth of those born to multiparae were entirely on formula feedings. Whether or not the cessation of nursing in many of these patients was voluntary on their part is not clear, but since the social status of the majority of them rendered profitable the prolongation of breast feeding it seems probable that the usual reason was an early cessation of adequate lactation in this race. Secondly, many women of both races who at discharge had an inadequate supply of milk necessitating supplementary feedings, now had a sufficient amount for the needs of their children, and this increase was noted to a greater degree in the

TABLE 4

Feeding of infants six weeks after birth (per cent of total number examined)

	PRIMIPARAE			MULTIPARAE		
	White	Black	Total	White	Black	Total
	per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
Maternal	73.76	92.86	86.24	76.00	92.12	84.66
Mixed	9.22	5.26	6.63	13.71	4.43	8.73
Artificial	17.02	1.88	7.13	10.29	3.45	6.61

black than in the white mothers. Finally, the number of babies on mixed feedings by this time had fallen greatly, and now comprised a part of the other two groups.

Table 5 illustrates the type of feeding of the infants at six weeks of age in relation to the type of feeding employed when they left the hospital. Obviously those children who were artificially fed at the earlier period were still on the same type of formula at this time. Moreover, when the supply of breast milk was already adequate ten to fourteen days after delivery, there was still sufficient for the babies' needs in the vast majority of cases.

It has long been a debated point as to whether or not it is wise to attempt to prolong nursing when the early supply of milk is insufficient. It has been the policy of the clinic to send infants of ward patients home on breast feeding even when considerable use of a supple-

mentary formula is necessary. Table 5 indicates the results of such a policy and would seem to prove that it is a valuable one, since 53 per cent of the white and 86 per cent of the black infants leaving the hospital on mixed feedings at six weeks after birth were entirely breast fed. The fact that a much greater number of negro women than white had developed an adequate lactation would seem to be explained by the facts that, in the main, the former is a definitely better nursing mother than the latter and also that the black woman seems more

TABLE 5

Feeding of children six weeks after birth in relation to type of feeding at time of discharge from hospital (per cent of total examined)

	FEEDING AT SIX WEEKS					
	Feeding at discharge, maternal			Feeding at discharge, mixed		
	White	Black	Total	White	Black	Total
	per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
Maternal	88.83	94.93	92.67	53.15	86.82	71.25
Mixed	3.05	3.28	3.20	25.23	8.53	16.25
Artificial	8.12	1.79	4.13	21.62	4.65	12.50

TABLE 6

Average duration of breast feeding

	WHITE	BLACK	TOTAL, BOTH RACES
	months	*months*	*months*
Primiparae	7.38	8.49	8.17
Multiparae	8.14	9.54	8.94
Total	7.75	8.84	8.47

easily upset generally by any change from her natural home environment. We feel as a result of this study that even though the supply of breast milk is definitely inadequate during the first two weeks after delivery it is profitable to insist on nursing being continued for a longer period.

The effect of race and parity on the total duration of lactation is shown in table 6 and figure 1. We use the word lactation advisedly since in our experience the majority of these patients do not stop

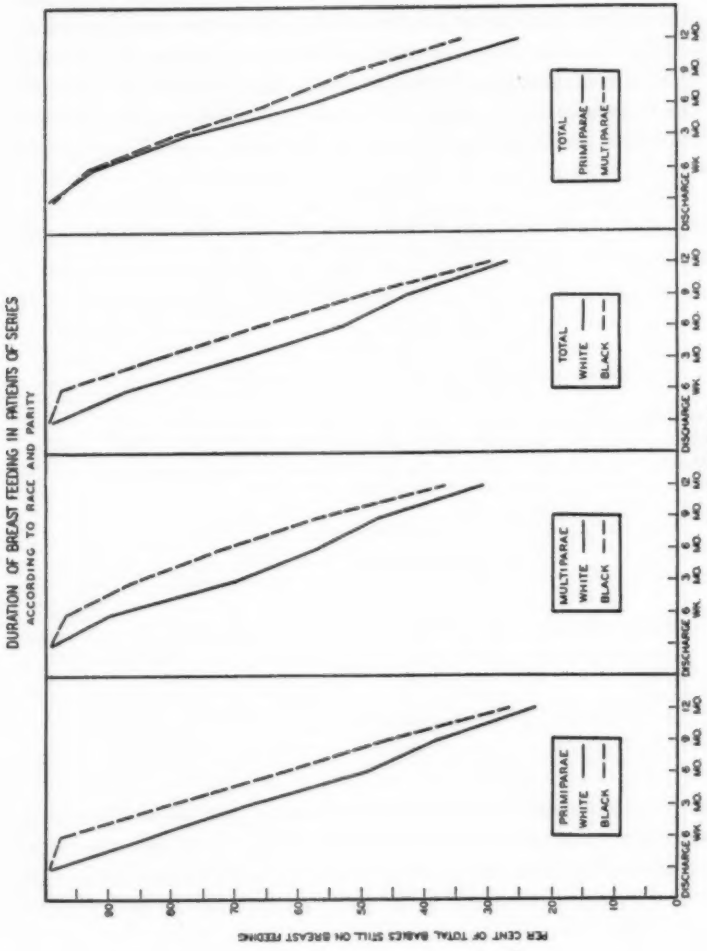
DURATION OF BREAST FEEDING IN PATIENTS OF SERIES
ACCORDING TO RACE AND PARITY
PER CENT OF TOTAL BABIES STILL ON BREAST FEEDING
TIME POST PARTUM
DISCHARGE
6 WK.
3 MO.
6 MO.
9 MO.
12 MO.
PRIMIPARAE
WHITE
BLACK
MULTIPARAE
WHITE
BLACK
TOTAL
WHITE
BLACK
TOTAL
PRIMIPARAE
MULTIPARAE

FIG. 1

nursing within a year unless lactation fails. From the charts it will be noted that 26 per cent of the white women and 29 per cent of the black women are still lactating twelve months after delivery. This function apparently persists longer in the black race and in our series lasted slightly over one month more than among the whites. Moreover, in both races the multiparous woman was able to continue nursing over a definitely longer period of time than the primiparous.

STATISTICS OF MOTHERS

The figures subsequently presented on the mothers of the series are based on those 2885 women returning for examination twelve to thirteen months after delivery. All of these women were examined at the time of discharge from the hospital and hence we have an equal series at this time. Less than half of them returned for examination six

TABLE 7

Outlet—tears. Discharge from hospital (per cent of total)

	PRIMIPARAE			MULTIPARAE		
	White	Black	Total	White	Black	Total
	per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
Perineum not torn.....	44.73	47.21	46.47	75.13	80.21	78.05
Perineum torn.....	55.27	52.79	53.53	24.87	19.79	21.95

weeks after delivery and hence some of the analyses based on results obtained at this time do not balance exactly with the other two. It is considered, however, that they approach closely enough to be comparable.

The incidence of perineal tears occurring at delivery is shown in table 7. It should be stated that during the time comprised in this study the routine use of episiotomy prior to the delivery of a primipara was not employed in the clinic, although it was sometimes used preceding certain operative procedures. No comment on this table seems necessary except to note that there seems to be a slightly greater risk of a lacerated perineum in the white woman, both primipara and multipara, than in the black.

The clinical impression as to results obtained following repair of perineal lacerations is shown in table 8. Frequently the tear, vaginal

or perineal, was of such small magnitude that repair was deemed unnecessary, and these cases have been omitted from the table. It will be noted that the repair was classed as poor in about a fourth of the white and a sixth of the black patients at the time of discharge from the hospital. This was intended to indicate that healing was not complete and hence a final decision as to result was impossible, rather than that infection or actual breaking down had occurred. At six weeks after delivery the number of repairs now definitely on the unsatisfactory side was small and was 5.68 and 3.14 per cent in the white and black patients, respectively. In view of the number of infected emergency cases in the series we feel that these results are fairly

TABLE 8

Outlet—repair (per cent of total)

	DISCHARGE FROM HOSPITAL			SIX WEEKS AFTER DELIVERY		
	White	Black	Total	White	Black	Total
	per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
Repair excellent.....	58.97	69.68	66.26	90.91	95.60	93.93
Repair good.....	17.52	13.65	14.89	3.41	1.26	2.02
Repair poor.....	23.50	16.67	18.85	5.68	3.14	4.05

satisfactory and would probably compare favorably with a series in which routine episiotomy had been employed.

The clinical impression as to the ultimate perineal result in terms of outlet relaxation is shown in table 9. It will be noted that at the time of discharge from the hospital 1.22 per cent of the primiparae and 18.75 per cent of the multiparae were believed to have marked relaxation. The percentage of whites in the latter group was twice as high as that of the blacks, although no such difference was noted in the primiparous population. The changing incidence of relaxation with increasing parity of the patient is shown in table 9 B. It is evident from a study of this table that many multiparae thought at discharge to have definite outlet relaxation were found a year after delivery to have recovered sufficient perineal tone so that the condition could be classified as "relaxation—none" or "slight;" the percentage with marked relaxation falling in the whites from 26.41 to 14.71 per cent and in the blacks from 13.17 to 5.58 per cent. Likewise, in both primiparae and multi-

TABLE 9

Outlet relaxation (per cent of total)

A. Discharge from hospital

	PRIMIPARAE			MULTIPARAE		
	White	Black	Total	White	Black	Total
	per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
None	74.55	76.16	75.69	35.73	46.18	41.77
Slight	24.16	22.65	23.09	37.86	40.65	39.48
Marked	1.30	1.19	1.22	26.41	13.17	18.75

B. Twelve months post-partum visit

WHITE	NONE	SLIGHT	MARKED
	per cent	*per cent*	*per cent*
Para 1	88.57	10.11	1.32
Para 2–3	60.87	30.80	8.33
Para 4–5	40.59	40.59	18.81
Para 6–7	41.25	36.25	22.50
Para 8 and over	29.11	46.84	24.05
Total multiparae	49.53	35.75	14.71
BLACK			
Para 1	88.20	10.49	1.31
Para 2–3	68.72	28.51	2.77
Para 4–5	51.69	42.37	5.93
Para 6–7	44.07	42.37	13.56
Para 8 and over	35.71	47.14	17.14
Total multiparae	60.67	33.75	5.58
TOTAL PATIENTS			
Para 1	88.31	10.37	1.31
Para 2–3	65.82	29.36	4.83
Para 4–5	46.58	41.55	11.87
Para 6–7	42.45	38.85	18.70
Para 8 and over	32.21	46.98	20.81
Total multiparae	55.90	34.61	9.49

parae, the number of patients having no relaxation at the end of a year was much higher than at delivery. Attention is drawn to the fact that the perineum of the black woman seems to stand the strain of repeated

child-bearing much better than that of the white. The only explanation that presents itself for this discrepancy lies in the smaller average size of the colored infant, but it is felt that this alone does not suffice and that probably we are dealing with a distinct racial difference. Finally, it will be noted that there is a definite increase in the percentage of relaxations found with advancing parity, and that among those women who have borne eight or more children a marked insufficiency of support was found in 24 per cent of the whites and 17 per cent of the blacks. From this study we would then infer that it is not wise to make a decision as to perineal relaxation and hence as to subsequent repair early in the puerperium, but should defer judgment until a much later date when as much support as is possible in a given case may have been recovered.

TABLE 10

Levator muscles twelve months after delivery (per cent of total)

	PRIMIPARAE			MULTIPARAE		
	White	Black	Total	White	Black	Total
	per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
Strong	85.54	86.49	86.20	73.98	79.43	77.18
Fair	9.24	8.95	9.04	17.07	12.57	14.43
Poor	5.22	4.56	4.76	8.94	8.00	8.39

The final item of information obtainable concerning the perineum in terms of efficiency of the levator muscles is shown in table 10. The figures given concern the clinical impression as to strength of the levators, and it will be noted that in 4.76 per cent of the total primiparae and 8.39 per cent of the multiparae it is classified as poor.

The incidence of cervical tears of sufficient degree to be readily demonstrable on pelvic examination is shown in table 11, which presents the results obtained both at the time of discharge from the hospital and twelve or more months after delivery. Laceration of the cervix at the time of the first delivery occurred in approximately four-fifths of the patients of both races, while in the multiparae it was found in 90.76 per cent of cases. Some time after delivery these tears healed entirely in a certain number of women so that at the year-return visit they were found in 61.74 per cent of the primiparae and 83.90 per cent

of the multiparae. The incidence of cervical tears was slightly but not definitely higher in the white than in the black race.

The degree of involution of the uterus determined at the time of discharge of the patient from the hospital and also six weeks *post partum* is shown in table 12. Since many of the women in the series returned

TABLE 11

Cervix (per cent of total)

	PRIMIPARAE			MULTIPARAE		
	White	Black	Total	White	Black	Total
A. Discharge from hospital						
	per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
Not torn	19.91	21.00	20.68	5.86	11.82	9.24
Torn	80.09	79.00	79.32	94.14	88.18	90.76
B. Twelve months after delivery						
Not torn	33.49	40.31	38.26	14.14	17.63	16.10
Torn	66.51	59.69	61.74	85.86	82.37	83.90

TABLE 12

Involution of uterus (per cent of total)

	PRIMIPARAE			MULTIPARAE		
	White	Black	Total	White	Black	Total
A. Discharge from hospital						
	per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
Well involuted	67.95	74.33	72.43	63.41	68.01	66.04
Poorly involuted	32.05	25.67	27.57	36.59	31.99	33.96
B. Six weeks after delivery						
Well involuted	89.44	89.71	89.62	85.95	88.70	87.50
Poorly involuted	10.56	10.29	10.38	14.05	11.30	12.50

to their homes as early as ten days after delivery it was not surprising to find in a large number the uterus classed as 'poorly involuted,' amounting to 27.57 per cent of the primiparae and 33.96 per cent of the multiparae. However, the finding that subinvolution existed in more than ten per cent of the patients six weeks after delivery was

unexpected, although it is probably explained by the fact that these patients, owing to their social conditions, were obliged to return to heavy household duties much earlier in the puerperium than was advisable. The increased incidence of faulty involution in the multiparae over the primiparae of the group was to be expected, but we see no reason why the uterus of the colored woman should have involuted more rapidly and efficiently than that of the white, although such was the case regardless of parity.

TABLE 13

Retroflexion of uterus (per cent of total)

	PRIMIPARAE			MULTIPARAE		
	White	Black	Total	White	Black	Total
A. Discharge from hospital						
	per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
Not retroflexed	97.29	97.89	97.71	97.25	97.80	97.57
Retroflexed	2.71	2.11	2.29	2.75	2.20	2.43

	WHITE	BLACK	TOTAL
B. Six weeks after delivery			
Not retroflexed	81.09	82.14	81.75
Retroflexed	18.91	17.86	18.25
C. Twelve months after delivery			
Not retroflexed	83.15	83.19	83.18
Retroflexed	16.85	16.81	16.82

The incidence of retroflexion of the uterus in terms of the three examinations under consideration is shown in table 13. For this item no essential differences were observed between the primiparae and multiparae of the series, nor between the whites and blacks. Since the discharge examination was done usually at about the ninth day of the puerperium while the uterus was still an abdominal organ, it was natural to find only a small percentage of retroflexions at this time. However, at six weeks after delivery 18.25 per cent of the patients showed this abnormality, and a year after delivery it was found in 16.82

per cent. Unfortunately, no figures are available to indicate in how many of the women the retroflexion had existed prior to the pregnancy.

In the great majority of the cases of retroflexion an attempt was made to correct this abnormality at the time when it was first found and the results of this manoeuver are shown in table 14. At the time of discharge from the hospital reposition was possible in 88.37 per cent of the cases, and most of the unsuccessful attempts were not at all vigorous because of a healing perineum. Unsuccessful results were obtained in 23.42 per cent of the cases found six weeks after delivery, while a year after delivery the figure had risen to 47.62 per cent. It

TABLE 14

Attempt to correct retroflexion

	WHITE	BLACK	TOTAL
A. Discharge from hospital			
Successful 88.37 per cent of attempts			
B. Six weeks after delivery			
	per cent	*per cent*	*per cent*
Brought forward	91.30	66.15	76.58
Unsuccessful	8.70	33.85	23.42
C. Twelve months after delivery			
Brought forward	56.25	49.12	52.38
Unsuccessful	43.75	50.88	47.62

will be noted that the uterus could be brought forward in a much greater number of the white than of black patients. It is our belief that this discrepancy lies in the greater lack of coöperation on the part of the black women to this painful procedure. It is, moreover, our opinion that correction should be done if necessary under anaesthesia since it seems evident that the chances of ultimate success are much greater the sooner after delivery it is effected.

Table 15 indicates the frequency with which the striae of pregnancy were found to have persisted on patients a year after delivery. Many striae were noted in approximately a fifth of the total number and were somewhat more frequent in the black than in the white race.

The incidence of faulty abdominal support in terms of diastasis of the rectus muscles persisting a year after delivery is detailed in table 16. In over half of the patients, including multiparae, no diastasis was observed, while the number with marked separation of the recti muscles was less than a tenth. This last figure seems surprisingly low

TABLE 15

Abdomen—striae, twelve months after delivery (per cent of total)

	WHITE	BLACK	TOTAL
	per cent	*per cent*	*per cent*
No striae	39.31	37.85	38.34
Few striae	43.01	39.58	40.72
Many striae	17.68	22.58	20.94

TABLE 16

Abdomen—diastasis, twelve months after delivery (per cent of total)

	WHITE	BLACK	TOTAL
	per cent	*per cent*	*per cent*
No diastasis	56.89	50.61	52.72
Slight diastasis	35.48	40.65	38.91
Marked diastasis	7.63	8.74	8.37

TABLE 17

Duration of lactation (per cent of total)

	WHITE	BLACK	TOTAL
	per cent	*per cent*	*per cent*
1–3 months	30.54	16.76	21.46
4–6 months	16.45	17.06	16.85
7–9 months	9.84	16.45	14.19
10–12 months	16.89	20.11	19.01
Lactating at end of twelve months	26.28	29.63	28.49

in view of the active existence assumed by most of the patients in the series within two weeks of the time of delivery.

Table 17 indicates the duration of lactation in the women comprising the series under discussion. This item has already been discussed under duration of breast feeding and is given here in order that it may be compared with figures to be shown subsequently con-

cerning the time of onset of menstruation after delivery. Two points however, seem worthy of reiteration, namely, that lactation lasted in the black race about a month longer than in the white, the mean figures obtained being 8.86 and 7.76 months, respectively; and that a year after delivery lactation was still present in 28.49 per cent of the total cases.

The time, in months after delivery, when menstruation recurred in the patients of the series is shown in table 18. It will be noted that at the end of one year only 10.85 per cent had failed to menstruate. The mean interval elapsing was 5.09 months in the white patients and 5.58 months in the black. Comparing these figures with the ones obtained from the previous table we find that on the average men-

TABLE 18

Onset of menstruation—months after delivery (per cent of total)

	WHITE	BLACK	TOTAL
	per cent	*per cent*	*per cent*
1 month	19.24	22.85	21.61
2 months	17.87	10.25	12.86
3 months	12.96	11.25	11.83
4–6 months	23.47	23.56	23.53
7–9 months	9.69	12.03	11.23
10–12 months	6.96	8.68	8.09
No recurrence at end of 12 months	9.82	11.39	10.85

struation recurred 2.67 months before lactation ceased in the white woman of the series, and 3.28 months before in the black.

The data accumulated on the relation between the cessation of lactation and the onset of menstruation are given in table 19. In the first portion of the table (A), it will be noted that the menses recurred more often before the cessation of lactation than after, 64.94 per cent in the white and 74.74 per cent in the black patients, respectively. Furthermore, the recurrence was often observed several months before nursing was stopped, and in more than a third of those women who menstruated while still lactating, it was observed seven or more months before the cessation of the latter function. On the other hand, when lactation ceased prior to the reëstablishment of the menstrual function the latter usually began relatively soon, in over 90 per cent of these pa-

tients within two months. Table D under this heading and also figure 2 indicate the percentage of patients in whom menstruation

TABLE 19

Relation between menstruation and lactation

ONSET OF MENSTRUATION	WHITE	BLACK	TOTAL
A. Relation of onset of menstruation to lactation (per cent of total)			
	per cent	*per cent*	*per cent*
Before cessation of lactation	64.94	74.74	71.45
After cessation of lactation	35.06	25.26	28.55
B. Time of onset of menstruation in months before cessation of lactation (per cent of total)			
1 month	16.28	14.10	14.77
2 months	13.37	11.13	11.82
3 months	11.34	11.51	11.46
4–6 months	24.42	27.94	26.86
7 months and over	34.59	35.32	35.09
C. Time of onset of menstruation in months after cessation of lactation (per cent of total)			
1 month	78.07	70.31	73.59
2 months	14.97	15.23	15.12
3 months	3.21	5.86	4.74
4 months and over	3.74	8.59	6.55
D. Relation of onset of menstruation to duration of lactation Menses recurred before cessation of lactation (per cent of total cases)			
DURATION OF LACTATION			
1 month	1.61	0.00	0.81
2 months	30.43	34.38	32.73
3 months	43.33	40.58	41.86
4 months	57.58	49.09	52.27
5 months	63.16	55.26	57.89
6 months	61.36	68.89	66.42
7–8 months	69.70	78.50	76.43
9–10 months	75.00	78.16	77.43
11–12 months	71.79	79.72	76.92
13 months and over	81.48	81.37	81.40

recurred before the cessation of lactation according to the duration of the latter. When nursing could be continued only a month, men-

struation had already recurred in less than one per cent of patients, a figure which for two months' lactation had risen to 32.73, and by the end of a year to 81.40 per cent.

Table 20 indicates that 24.70 per cent of the white and 33.51 per cent of the black patients became pregnant again during the first year

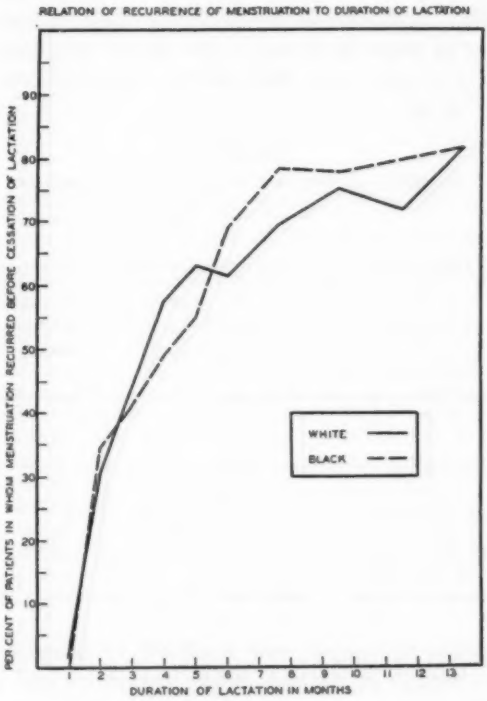

FIG. 2

after delivery. In an appreciable number of them the pregnancy had already terminated, either in abortion or full term delivery, prior to the year-return visit. The time in months after delivery when pregnancy began is also noted in the table. The last set of figures given, for ten months after delivery and over, is considered somewhat inaccurate since there were probably a number of early unrecognized

pregnancies in these cases which should form part of this group. The table demonstrates the frequency which with too closely spaced childbearing occurs in women of the poorer social strata.

It is interesting to note that among those women of the series who again became pregnant during the first year after delivery, 35.75 of the whites and 46.98 per cent of the blacks were still lactating at the time of conception. Moreover, although half of these patients had menstruated four or more times before the second pregnancy occurred, approximately a tenth of the total number conceived without having menstruated at all.

TABLE 20

Pregnancy occurring in first twelve months after delivery

	WHITE	BLACK	TOTAL
A. Pregnant at or before year return (per cent of total patients)			
	per cent	*per cent*	*per cent*
Pregnancy	24.70	33.51	30.38
No pregnancy	75.30	66.49	69.62
B. Months after delivery at onset of pregnancy (per cent of total pregnant patients)			
1 month	0.82	0.84	0.84
2 months	1.65	1.51	1.55
3 months	8.64	5.19	6.21
4–6 months	29.63	32.83	31.86
7–9 months	37.04	36.68	36.75
10 months* and over	22.22	22.95	22.79

* Figures inaccurate because of early undiagnosed pregnancies at year return visit.

Unfortunately no figures were available to afford a comparison between the weight of patients before pregnancy and a year after delivery. However, we are able to compare the latter weight with that obtained at the time of discharge from the hospital and this is shown in table 21. Approximately a third of the total patients, white and black, primiparae and multiparae, showed a loss of weight. On the other hand, 47.36 per cent of the primiparae and 56.53 per cent of the multiparae had gained a varying amount. The multiparae showed a greater tendency to gain weight after pregnancy than the primiparae, and this was noticeable to a greater degree in the black than

in the white women. About a quarter of the multiparae were fifteen or more pounds heavier a year after delivery than at the time of discharge from the hospital, whereas a similar increase was noted in only a sixth of the primiparae of the series.

At the time of the year-return examination the patients were asked whether or not, in their opinion, there was any alteration in their general health after the pregnancy from that which it had been before.

TABLE 21

Relation of weight twelve months after delivery to weight at time of discharge from hospital

	PRIMIPARAE			MULTIPARAE		
	White	Black	Total	White	Black	Total
	per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
Loss of weight	37.87	34.39	35.50	38.28	25.32	31.01
No change	13.91	18.65	17.14	11.22	13.44	12.46
Gain— 1–4 pounds	5.03	6.91	6.31	4.29	6.72	5.65
Gain— 5–9 pounds	13.61	10.91	11.77	10.56	11.63	11.16
Gain—10–14 pounds	6.80	9.81	8.85	11.22	11.89	11.59
Gain—15 pounds and over	17.46	16.30	16.67	22.77	28.94	26.23
Gain—amount unknown	5.33	3.04	3.77	1.65	2.07	1.88

TABLE 22

Patients' impression as to health twelve months after delivery in relation to health before pregnancy

	PRIMIPARAE			MULTIPARAE		
	White	Black	Total	White	Black	Total
	per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
No change	94.16	96.70	95.94	89.31	94.25	92.15
Improved	2.16	0.92	1.29	1.09	0.40	0.69
Worse	3.68	2.38	2.77	9.60	5.35	7.15

In the vast majority there had been noted no appreciable changes' 95.94 per cent of the primiparae and 92.15 per cent of the multiparae. A very few of the women felt that their health had been improved and most of these had been delivered of their first baby. However, 2.77 per cent of the primiparae and 7.15 per cent of the multiparae of the series felt that their physical condition had been definitely altered for the worse, and among them the majority were of the white race. It is surpris-

ing that with the too rapid resumption of household duties in unfavorable surroundings on the part of these patients, and the rapidly recurring pregnancies of many of them, a larger percentage did not feel a deleterious effect following pregnancy and labor. The fact that more than nine-tenths of the total number could find no alteration in their health a year after delivery is a reassuring one, indicating that the average pregnancy with proper supervision is a normal physiological process, an axiom that in modern obstetrics tends all too frequently to be forgotten.

SUMMARY

In the foregoing study of 2885 patients reëxamined twelve or more months subsequent to delivery in the Johns Hopkins Hospital, we have endeavored to present certain items of information on mother and child from a statistical point of view and have not stressed conclusions which might be drawn from them. It must be emphasized that the patients in the series, both white and black, are entirely public ward material and come from an extremely low social and economic environment.

In summarizing the study it would seem that certain generalizations might profitably be made.

1. The stillborn and neonatal mortality rates were high, even for a clinic population with a large percentage of referred emergency cases. If the community could be educated so that women would apply early for prenatal care, and after delivery would attend regularly the child welfare clinics extant in most large cities, the rates would be lowered appreciably.

2. The black women were more successful in nursing their babies and could continue this function for a longer period of time than the whites. Lactation also lasted longer in the multiparae than in the primiparae.

3. The percentage of nursing mothers was high. Even if the supply of breast milk was insufficient for the baby's needs ten to fourteen days after delivery it often became adequate later in the puerperium. In this series, 28.49 per cent of the women were still nursing at the end of a year.

4. The incidence of perineal tears, relaxed vaginal outlets, cervical

tears, and subinvolution of the uterus were greater in the white than in the black race. The ultimate result to the perineum in a series of cases not treated by routine episiotomy was good, only 1.31 per cent of the primiparae being left with marked relaxations. Probably as a result of the too rapid resumption of household duties on the part of the patients ten per cent of the primiparae and twelve per cent of the multiparae still had definite subinvolution six weeks after delivery.

5. About a sixth of the total number of patients had retroflexed uteri a year after delivery. The earlier in the puerperium an attempt is made to correct this abnormality the greater are the chances of the manoeuver being successful.

6. Only 8.37 per cent of the women, including multiparae, were left with faulty abdominal support as evidenced by diastasis of the rectus muscles.

7. In 71.45 per cent of the cases menstruation recurred before the cessation of lactation, and in more than a third of these preceded it by seven or more months. However, when lactation ceased first, the menses were usually established within two months. For the total series the average duration of lactation was almost three months more than the mean time interval between delivery and menstruation.

8. A fourth of the white patients and a third of the blacks again became pregnant in the first year after delivery. This figure is probably somewhat too low because of the early pregnancies often unrecognized at the year-return examination.

9. 47.36 per cent of the primiparae and 56.53 per cent of the multiparae showed a gain of weight during the year after delivery in relation to the figure obtained at the time of discharge from the hospital. This tendency to gain was greater in the blacks than in the whites of the series.

10. 96 per cent of the primiparae and 92 per cent of the multiparae noted no change in their general health as a result of the pregnancy. In only 2.77 per cent of the former and 7.15 per cent of the latter was it felt that the child-bearing had had a deleterious effect. It is felt that this is a very low figure, since these patients because of their social and economic environment might be expected to fare worse than the more sheltered women of the upper and middle classes.

THE EFFECT OF HEMISECTION OF THE COCHLEAR BRANCH OF THE HUMAN AUDITORY NERVE. PRELIMINARY REPORT

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In earlier publications it has been observed that after hemisection of the sensory root of the fifth nerve, practically no disturbance of sensation resulted. At a later date a patient whose optic nerve had been divided in more than half of its cross section the vision returned to normal following the removal of an hypophyseal tumor; in fact no difference could be determined between the vision of the intact and of the partially severed optic nerve.

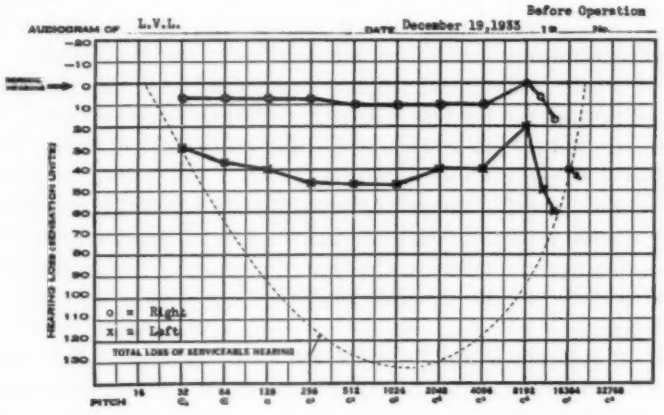

FIG. 1. AUDIOGRAM BEFORE HEMISECTION OF THE COCHLEAR DIVISION OF THE AUDITORY NERVE

This note is concerned with further evidence of much the same character after partial section of the auditory nerve. The patient,

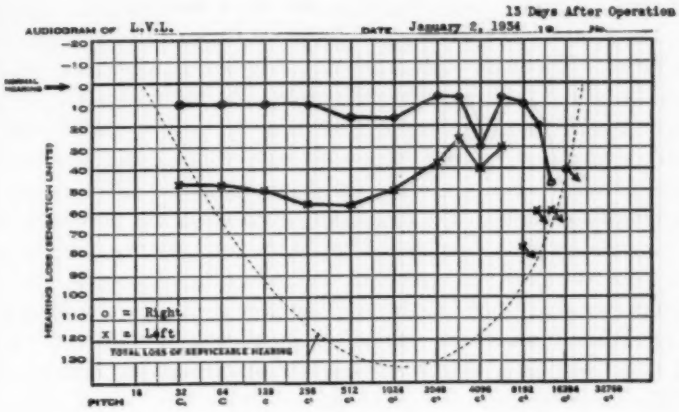

FIG. 2

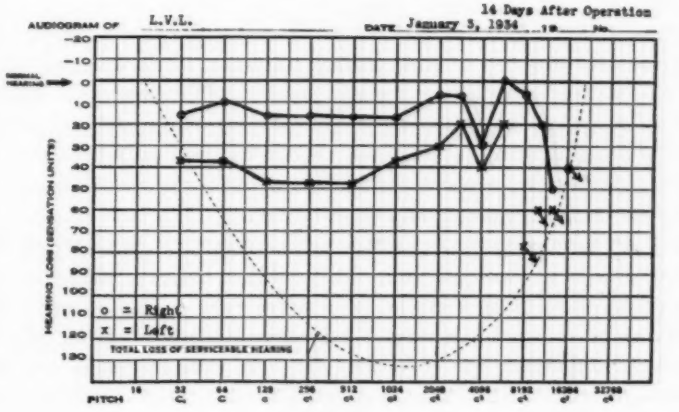

FIG. 3

FIGS. 2 AND 3. AUDIOGRAMS THIRTEEN AND FOURTEEN DAYS, RESPECTIVELY, AFTER HEMISECTION OF THE COCHLEAR DIVISION OF THE AUDITORY NERVE

F., aged forty-four years, was operated upon for Ménière's disease, the left auditory nerve being divided in three-fourths to four-fifths of its extent. From an earlier experience in which five-eights of the acoustic nerve—all of the vestibular branch and one-eighth of the cochlear—had been sectioned, there was no post-operative loss of hearing whatever. When section of the vestibular and part of the cochlear branches of the nerve had been completed (there being no dividing lines between the component divisions of the nerve), it was my impression that about four-fifths of the total volume of the nerve had been sectioned; my assistant was asked for his opinion, and he volunteered that three-fourths of it had been divided; certainly it was not less than this amount. From this interpretation it is evident that all of the vestibular branch and one-half of the cochlear branch were divided, provided, of course, that the auditory nerve is equally divided by volume into the two branches.

Thirteen days after the operation the audiogram showed that all of the tones up to 6144 were almost exactly the same as before the operation; only the higher tones, 8192 and 12286, were lost. The highest tone, 16384, was absent both before and after the operation. On the following day another audiogram was made in order to check these findings and with identical results. The immediate result, therefore, following section of one-half, at least, of the cochlear branch of the acoustic nerve is loss of only two of the very high tones. This finding is seemingly in complete harmony with the results of partial division of the trigeminal and optic nerves.

I have no desire to speculate in generalizations concerning the significance of data of this character. It is evident, however, that there is a redundant supply of fibers in the sensory root of this as well as in that of other cranial nerves. It is also obvious that the ganglia mediate important functions and that the sensory roots lack the detailed service that obtains in the peripheral nerves. I also feel that it is difficult to harmonize such physiological facts with the neurone theory.

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